1 Clinical pharmacology of ageing

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EPIDEMIOLOGY

Trends in population ageing

In 2000, the worldwide population of those aged ≥65 years was an estimated 420 million, a 9.5 million increase from 1999. During the period 2000–2030, the worldwide population aged ≥65 years is projected to increase by approximately 550 million to 973 million, increasing from 6.9 % to 12.0 % worldwide, from 15.5 % to 24.3 % in Europe, from 12.6 % to 20.3 % in North America, and from 6.0 % to 12.0 % in Asia. The largest increases in absolute numbers of elderly people will occur in developing countries.

The ageing of the world’s population is the result of two factors: declines in fertility and increases in life expectancy. Life expectancy in developed countries now ranges from 76 to 80 years and also has increased in developing countries since 1950. A higher life expectancy at birth for females compared with males is almost universal, approximately seven years in Europe and North America but less in developing countries.

The world has experienced an epidemiological transition in the leading causes of death, from infectious disease and acute illness to chronic disease and degenerative illness. Developed countries in North America, Europe, and the Western Pacific already have undergone this transition, and other countries are at different stages of progression. The epidemiological transition, combined with the increasing number of older people, represents a challenge for public health. In the United States, approximately 80 % of all people aged ≥65 years have at least one chronic condition, and 50 % have at least two.

The increased number of older people will lead to increased healthcare costs. The healthcare cost per capita for those aged ≥65 years in developed countries is three to five times greater than the cost for those aged <65 years, and the rapid growth in the number of older people, coupled with continued advances in medical technology, is expected to create increasing pressure on health and long-term care spending.

Medication use in elderly patients

Safe and effective pharmacotherapy remains one of the greatest challenges in geriatric medicine. Elderly patients often suffer from several chronic disorders and consequently use more drugs than any other age group. The diminished physiological reserve associated
with ageing can be further depleted by effects of drugs and acute or chronic disease states. Ageing alters the pharmacokinetics and pharmacodynamics of many drugs. In addition, pharmacotherapy may be complicated by difficulties with obtaining drugs or complying with drug regimens.

In most developed countries, about two thirds of the population ≥65 years take prescription and nonprescription over the counter (OTC) drugs. At any given time, an average elderly person uses four to five prescription drugs and 2 OTC drugs and fills 12–17 prescriptions a year. The frail elderly patient uses the most drugs. Drug use is greater in hospitals and nursing homes than in the community; typically, a nursing home resident receives at least seven to eight drugs.

The type of drug used varies with the setting. Community patients use analgesics, diuretics, cardiovascular drugs, and sedatives most often; nursing home residents use antipsychotics and sedative-hypnotics most commonly, followed by diuretics, antihypertensives, analgesics, cardiac drugs, and antibiotics. Psychoactive drugs are prescribed for ∼65% of nursing home patients and for ∼55% of residential care patients; ∼7% of patients in nursing homes receive ≥ three psychoactive drugs concurrently.

Many drugs benefit elderly patients. Some can be life-saving (i.e., antibiotics and thrombolytic therapy). Oral hypoglycemic agents can improve independence and quality of life while controlling chronic disease. Antihypertensive drugs and influenza vaccines can help prevent or decrease morbidity. Analgesics and antidepressants can control debilitating symptoms. Therefore, appropriateness, that is whether the potential benefits outweigh the potential risks, should guide therapy.

AGE-RELATED CHANGES IN PHARMACOKINETICS

Drug absorption

Pharmacokinetic studies on the effect of ageing on drug absorption have provided conflicting results. Several studies have not shown age-related differences in absorption rates for different drugs (1). However, other studies have shown a reduced absorption of vitamin B12, iron and calcium and an increased absorption of the drug levodopa. For drugs absorbed by passive diffusion there is little evidence for an age related decline.

First-pass metabolism and bioavailability

There is a reduction in first-pass metabolism with advancing age. This is probably due to a reduction in liver mass and, for high clearance drugs, the consequential reduction in blood flow. The bioavailability of drugs undergoing extensive first-pass metabolism can be significantly increased. By contrast, the first-pass activation of several pro-drugs, such as the ACE inhibitors enalapril and perindopril, might be slowed or reduced (2).

Drug distribution

Significant changes in body composition occur with advancing age, such as a progressive reduction in the proportion of total body water and lean body mass (3). This results in a relative increase in body fat. Polar drugs that are mainly water-soluble tend to have smaller volumes of distribution (V) resulting in higher serum levels in older people (e.g. gentamicin, digoxin, lithium, and theophylline). By contrast, non-polar compounds (e.g. benzodiazepines, morphine and amiodarone) tend to be lipid-soluble and so their V increases with age. The main effect of the increased V is a prolongation of half-life. Increased V and elimination half life (t1/2z) have been observed for drugs such as diazepam, thiopental, lidocaine, and clomethiazole (4). The reduction in V for water-soluble drugs tends to be balanced by a larger reduction in renal clearance (CL), with a smaller effect on t1/2z, as shown in the following equation:

$$t_{1/2z} = \frac{\ln(2) \cdot V}{CL}$$

where $t_{1/2z}$ = elimination half-life, $\ln(2)$ = natural log of 2 (0.693), $V$ = apparent volume of distribution, and $CL$ = clearance.
Protein binding

Acidic compounds (e.g. diazepam, phenytoin, warfarin, salicylic acid) bind mainly to albumin whereas basic drugs (e.g. lidocaine, propranolol) bind to alpha-1 acid glycoprotein. Although no substantial age-related changes in the concentrations of both these proteins have been observed, albumin is commonly reduced in malnutrition or acute illness whereas alpha-1 acid glycoprotein is increased during acute illness. The main factor determining drug effect is the free concentration of the drug. Although plasma protein binding changes might theoretically contribute to drug interactions or physiological effects for drugs that are highly protein-bound, its clinical relevance is probably limited (5).

Drug clearance

Kidney

The age-related reduction in glomerular filtration rate affects the clearance of many drugs such as water-soluble antibiotics, diuretics, digoxin, water-soluble beta-blockers, lithium, and some non-steroidal anti-inflammatory drugs. The clinical importance of such reductions of renal excretion is dependent on the likely toxicity of the drug. Drugs with a narrow therapeutic index like aminoglycoside antibiotics, digoxin, and lithium are likely to have serious adverse effects if they accumulate only marginally more than intended. In elderly patients serum creatinine may be within the reference limits, while renal function is markedly diminished. The Cockcroft and Gault (6) or the Modification of Diet in Renal Disease (7) equations both use serum creatinine, age and gender and may be helpful for a better estimation of glomerular filtration rate in this situation.

Liver

Drug clearance by the liver depends on the capacity of the liver to extract the drug from the blood passing through the organ (hepatic extraction ratio) and hepatic blood flow. Drugs can be classified into three groups according to their extraction ratio (E): high (E > 0.7, such as clomethiazole, dextropropoxyphene, glyceryl trinitrate, lidocaine, pethidine, and propranolol), intermediate (E 0.3–0.7, such as aspirin, codeine, morphine, and triazolam), and low extraction ratio (E < 0.3, such as carbamazepine, diazepam, phenytoin, theophylline, and warfarin). When E is high, the clearance is rate-limited by blood flow. When E is low, changes in blood flow produce little changes in clearance. Therefore, the reduction in liver blood flow with ageing affects mainly the clearance of drugs with a high extraction ratio. Of much greater importance is the reduction in liver volume of as much as 30% across the adult age range. This results in a reduction in clearance of a similar magnitude (8).

Several studies have shown significant age-related reductions in the clearance of many drugs metabolized by phase-1 pathways in the liver. These involve reactions such as oxidation and reduction. By contrast, phase-2 pathways (e.g. glucuronidation) do not seem to be significantly affected (8).

AGE-RELATED CHANGES IN PHARMACODYNAMICS

Studies of drug sensitivity require measurement of concentrations of drug in plasma, as well as measurement of drug effects. This is because changes in pharmacokinetics with increasing age may result in changes in response due purely to the changes in drug concentrations. Some important pharmacodynamic age-related changes are illustrated in Table 1.1.

Anticoagulants

There is evidence of a greater inhibition of synthesis of activated vitamin K-dependent clotting factors at similar plasma concentrations of warfarin in elderly compared to young patients. However, the exact mechanisms responsible for the increased sensitivity are unknown.

Cardiovascular and respiratory drugs

Although elderly subjects are less sensitive to the effects of verapamil on cardiac conduction,
### Table 1.1. Selected pharmacodynamic changes with ageing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacodynamic effect</th>
<th>Age-related change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Heart-rate response</td>
<td>↔</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Sedation, postural sway</td>
<td>↑</td>
</tr>
<tr>
<td>Diltiazem,</td>
<td>Acute and chronic antihypertensive effect</td>
<td>↑</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Acute PR interval prolongation</td>
<td>↓</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Postural sway</td>
<td>↔</td>
</tr>
<tr>
<td>Enalapril</td>
<td>ACE inhibition</td>
<td>↔</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Peak diuretic response</td>
<td>↓</td>
</tr>
<tr>
<td>Heparin</td>
<td>Anticoagulant effect</td>
<td>↔</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>Chronotropic effect</td>
<td>↓</td>
</tr>
<tr>
<td>Morphine</td>
<td>Analgesic effect</td>
<td>↑</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Respiratory depression</td>
<td>↔</td>
</tr>
<tr>
<td>Propranolol</td>
<td>α1-adrenergic agonism</td>
<td>↔</td>
</tr>
<tr>
<td>Scopolamine (hyoscine)</td>
<td>Cognitive function</td>
<td>↓</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Postural sway</td>
<td>↑</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Anticoagulant effect</td>
<td>↑</td>
</tr>
</tbody>
</table>

Legend: ↑ = increase; ↓ = decrease; ↔ = no significant change; ACE = angiotensin-converting enzyme.

the effect on blood pressure and heart rate tends to be greater in older than in younger patients. This might be explained by an increased sensitivity to the negative inotropic and vasodilator effects of verapamil as well as diminished baroreceptor sensitivity. The acute intravenous administration of diltiazem causes greater prolongation of the PR interval (dromotropic effect) in young than in elderly subjects. Reduced β-adrenoceptor function is observed with advancing age. Elderly patients are less sensitive to the chronotropic effect of isoprenaline. The impaired response, however, is due primarily to an age-related reduction in the influence of reflex cardiovascular effects on heart rate rather than reduced β-adrenergic sensitivity. Both salbutamol (β-agonist) and propranolol (β-antagonist) show reduced responses with age. This is secondary to impaired β-receptor function due to reduced synthesis of cyclic AMP following receptor stimulation. The total number of receptors seems to be maintained but the post-receptor events are changed because of alterations of the intracellular environment. The responsiveness of α-adrenoceptors is preserved with advancing age.

### Psychotropic drugs

Elderly patients are particularly vulnerable to adverse effects of neuroleptics, such as extrapyramidal symptoms, arrhythmias, and postural hypotension. Agents with anticholinergic effects can also impair cognition and orientation in patients with a cholinergic deficit such as those with Alzheimer’s disease. Advancing age is also associated with increased sensitivity to the central nervous system effects of benzodiazepines. The exact mechanisms responsible for the increased sensitivity to these drugs with ageing are unknown, however.

### Adverse Drug Reactions and Drug Interactions

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality in elderly patients. It is not clear however whether advancing age per se is a cause of increased risk of ADRs. Nursing home and frail elderly patients appear to be at high risk of ADRs (9).

Although around 10% of the general population take more than one prescribed medicine,
the incidence of combination therapy is greatest in the elderly, in females, and in those who have had a recent hospital admission. Patients aged >65 years use on average four prescribed medications. A list of common drug interactions in elderly patients is illustrated in Table 1.2.

The risk of ADRs is exponentially rather than linearly related to the number of medicines taken. More than 80% of ADRs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Impact</th>
<th>Mechanism of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>NSAIDs</td>
<td>Potential for serious gastrointestinal bleeding</td>
<td>NSAIDs increase gastric irritation and erosion of the protective lining of the stomach and decrease platelet function during clot formation</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Sulfa drugs</td>
<td>Increased effects of warfarin, with potential for bleeding</td>
<td>Warfarin’s activity maybe prolonged due to a decreased production of vitamin K by intestinal flora during sulfa drug administration</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Macrolides</td>
<td>Increased effects of warfarin, with potential for bleeding</td>
<td>Macrolides inhibit the metabolism of warfarin. The activity of warfarin may also be prolonged due to alterations in the intestinal flora and its production of vitamin K for clotting factor production</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Quinolones</td>
<td>Increased effects of warfarin, with potential for bleeding</td>
<td>The exact mechanism for the warfarin-quinolone drug interaction is unknown. Reduction of intestinal flora responsible for vitamin K production by antibiotics is probable as well as decreased metabolism of Warfarin</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Phenytoin</td>
<td>Increased effects of warfarin and/or phenytoin</td>
<td>Currently unknown, but one theory suggests a genetic basis involving liver metabolism of warfarin and phenytoin</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Potassium supplements</td>
<td>Elevated serum potassium</td>
<td>Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion.</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Aldosterone antagonists and potassium sparing diuretics</td>
<td>Elevated serum potassium</td>
<td>Additive effects on reduced potassium elimination</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Amiodarone</td>
<td>Digoxin toxicity</td>
<td>Multiple theories exist, but actual mechanism is unknown. Amiodarone may decrease the clearance of digoxin, resulting in prolonged digoxin half-life. There may also be an additive effect on the sinus node activity.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Verapamil</td>
<td>Bradycardia and heart block</td>
<td>Synergistic effect on sinus node and atrioventricular node</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Quinolones</td>
<td>Theophylline toxicity</td>
<td>Inhibition of hepatic metabolism of theophylline by the quinolones</td>
</tr>
</tbody>
</table>
causing admission or occurring in hospital are type A, i.e. they are dose related, predictable and potentially avoidable. Antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, antineoplastic agents and nonsteroidal anti-inflammatory drugs are mainly responsible for type-A ADRs. Type-B ADRs (idiosyncratic reactions) are less common but can be associated with serious toxicity (e.g. hepatotoxicity with flucloxacillin and co-amoxiclav; anaphylactic shock with penicillins).

**ADHERENCE**

Although the term compliance has gone out of fashion, in practice the three terms compliance, concordance and adherence all refer to the extent to which patients comply with the drug regimen they agreed with the prescriber. We will use the word adherence here.

The efficacy and safety of medicines is largely determined by adherence. Adherence is defined as the extent to which a person's behaviour, taking medication, following a diet, and/or executing life-style changes, corresponds with recommendations agreed with a health-care provider (10). Poor adherence to the treatment of chronic disease is an important problem. One of the first articles pointing at the lack of adherence was published in 1957; in only 50% of the patients who were prescribed tuberculostatics was the drug was found in urine (11). More recently a Cochrane review found 50% non-adherence in patients using medicines for chronic diseases (12). Adherence to antihypertensives and statin therapy is often even lower. Within one year of the start of antihypertensives 50% of the patients have stopped using these drugs (13). The adherence of elderly patients, prescribed statins, is 60% after three months, 43% after six months and 26% after five years (14).

The consequences of non-adherence are considerable including hospital admissions (33–60% of drug related hospital admissions) and higher mortality (15, 16). Even with use of placebo, high adherence had a 3.5 times greater effect on reducing mortality than the overall active treatment with candesartan in chronic heart failure (17). This finding suggests that high adherence for taking medicines, is associated with high adherence for life-style advice.

The identification of patient non-adherence is important. Factors that contribute to poor adherence are summarized in Table 1.3 (18). In general practice non-adherence is often detected by looking in the medicines cupboard at home. Another method makes use of pharmacy refill records comparing the number of dispensed doses with the number of prescribed doses. A very helpful starting point is to ask the patient and family for the problems they encountered with the drug regimen. The patient should not be blamed for poor adherence. The ability of patients to follow treatment plans is frequently compromised by several factors, including the characteristics of the disease (e.g. cognitive impairment), social system, heath care system, economic factors and patient-related factors. A tool for screening patient adherence is the Brief Medication Questionnaire (19). The Medication Event Monitoring System (MEMS) is an electronic device which records the time and date when a medication container was opened. These devices are used in controlled studies and not in daily practice, because of the expense. Other methods for detecting non-adherence are physiological markers, like low heart-rate with use of beta-blockers, or biochemical measurements in blood or urine Such as plasma angiotensin converting enzyme assays to monitor ACEI adherence.

Several methods have been shown to improve adherence. The most effective approach is multi-level targeting at several factors with several interventions. However effective interventions are often complex and not suitable for daily practice. Education in self-management of the drug regimen has limited effects. A simple and very effective method is the reduction of dose frequency. Adherence is found the highest with a dose frequency of once a day (79%), decreasing to 69% with b.i.d., 65% with t.i.d and 51% with q.i.d (20).

Integrating the patient’s perspective into treatment plans is considered very important.
Table 1.3. Methods of measuring adherence (adapted from Ref (18))

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly observed therapy</td>
<td>Most accurate</td>
<td>Patients can hide pills in mouth and then discard them; impractical for routine use</td>
</tr>
<tr>
<td>Biochemical measurement of the medicine or metabolite or measurement of a biological marker</td>
<td>Objective</td>
<td>Variations in metabolism and “white coat” adherence can give a false impression; expensive</td>
</tr>
<tr>
<td>Patient questionnaires or self-reports</td>
<td>Simple, inexpensive, most useful in clinical practice</td>
<td>Susceptible to error and distortion</td>
</tr>
<tr>
<td>Pill counts</td>
<td>Objective, quantifiable and easy to perform</td>
<td>Data easily altered by the patient (e.g. pill dumping)</td>
</tr>
<tr>
<td>Rates of prescription refills</td>
<td>Objective, easy to obtain data</td>
<td>A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system</td>
</tr>
<tr>
<td>Assessment of the patient’s clinical response</td>
<td>Simple; easy to perform</td>
<td>Factors other than medication adherence can affect clinical response</td>
</tr>
<tr>
<td>Electronic medication monitors</td>
<td>Precise; results are easily quantified; tracks patterns of taking medication</td>
<td>Expensive; requires return visits</td>
</tr>
<tr>
<td>Measurement of physiologic markers</td>
<td>Often easy to perform</td>
<td>Marker may be absent for other reasons</td>
</tr>
<tr>
<td>Patient diaries</td>
<td>Help to correct for poor recall; simple; objective</td>
<td>Easily altered by the patient</td>
</tr>
<tr>
<td>Questionnaire for caregiver, for patients who are cognitively impaired.</td>
<td>Help to correct for poor recall; simple; objective</td>
<td>Susceptible to error and distortion</td>
</tr>
</tbody>
</table>

The behaviour of prescribers is changing from a paternalistic one-way style towards concordance to improve adherence (21).

POLYPHARMACY VERSUS APPROPRIATE PRESCRIBING

Polypharmacy, often defined as the concurrent use of five or more different drugs, is common among elderly patients. Inappropriate polypharmacy contributes to unwanted and often preventable clinically relevant drug-drug and drug-disease interactions as well as adverse drug reactions (ADRs). Around 12% of elderly patients in hospitals are admitted because of ADRs (22). It is estimated that about 47–72% of these ADRs are avoidable (23, 25). Polypharmacy itself is not necessarily undesirable.

Polypharmacy, however, is a concept that addresses only the inappropriate use of medication. The term appropriate prescribing addresses the problems of both inappropriate use of medication as well as inappropriate non use of medication (or undertreatment).

OVER-THE-COUNTER MEDICINES

Elderly people are the largest consumers of over-the-counter (OTC) medicines. The switch of prescription drugs to OTC medicines is encouraged. Government policies make it possible to obtain increasing numbers of former prescription drugs from pharmacies, health food shops, supermarkets or by mail-order. The goal is to provide greater choice for individuals and to shift the responsibility for health care as well as the costs to individuals. The approach to OTC medicines varies between countries. In general it is considered that OTC can be used for short-term self-limiting illnesses with lower doses of commonly prescribed drugs and should have few important adverse effects.
Some consider herbal drugs, vitamins and minerals also as OTC drugs.

Older people use OTC medicines to treat minor complaints such as pain, constipation, colds and gastro-intestinal symptoms (25). The most commonly used OTCs are aspirin, paracetamol, NSAIDs, antihistamines and histamine H2 receptor antagonists. Recently in several countries statins are also available OTC. There are concerns regarding the safety of OTC medicines, especially in elderly patients. In particular, NSAIDs may cause gastrointestinal toxicity and sedatives, increase may the risk of falls. The use of multiple medications increases the risk of drug interactions and adverse effects. Cebollero-Santamaria et al. showed that bleeding from a peptic ulcer was associated with the use of NSAIDs in 81 % of 84 patients and that 95 % had purchased their NSAIDs OTC (26). The use of recommended doses of OTC NSAIDs has a relatively good safety profile compared to prescription NSAIDs, however patients may take higher doses for a longer period with serious gastrointestinal toxicity as a result (27). Many older people use OTC drugs to improve their sleep. The risks associated with this use have not been examined (25). Also the problems in older people with OTC H2 receptor antagonists, such as confusion, and OTC statins, such as liver and skeletal muscle toxicity, are not clearly defined.

Documentation of OTC medicines is poor. A study showed that only 5 % of OTC drugs, used by patients prior to and during hospitalization, were recorded on drug charts (28). Asking elderly patients, especially those admitted to hospitals, for their use of OTC drugs is important to prevent double-prescription and clinically relevant interactions. This applies also to herbal drugs as St. John’s wort. St. John’s wort is used to treat depressive symptoms. It induces the metabolism of several drugs and diminishes the absorption of digoxin (Table 1.4) (29). Other possible interactions are the diminishing effect of warfarin caused by cranberry juice and Ginseng (30, 31).

The increasing availability of OTC drugs clearly has benefits. Nevertheless, prescribers must always pay close attention to concomitant OTC medication use in order to minimize adverse drug reactions.

Table 1.4. Interactions with St. John’s wort (adapted from Ref (29))

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>Steady-state concentration decreased by 22%</td>
</tr>
<tr>
<td>ciclosporine</td>
<td>Steady-state concentration decreased by 52%</td>
</tr>
<tr>
<td>digoxin</td>
<td>Steady-state concentration decreased by 25%</td>
</tr>
<tr>
<td>simvastatin</td>
<td>AUC decreased by 50%</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>Steady-state concentration decreased by 80%</td>
</tr>
<tr>
<td>theophylline</td>
<td>Steady state concentration decreased by 50%</td>
</tr>
<tr>
<td>cumarin derivatives</td>
<td>INR 50% lower</td>
</tr>
</tbody>
</table>

AUC = Area under plasma concentration time curve

Clinical audit is fundamental to providing a high quality service. This is particularly true for prescribing. A variety of approaches have been advocated ranging from the use of purely descriptive prescribing indicators through application of consensus guidelines to strictly evidence based approaches. The use of purely descriptive approaches alone achieves little but is a useful adjunct to comparing observed prescribing to a gold standard.

Oborne et al. (1997) have described three types of prescribing indicator for use in prescribing audit (45). Purely descriptive indicators include mean numbers of drugs prescribed and numbers of drugs classified in the British National Formulary as “Black Triangle” drugs (7). These are recently introduced drugs for which all adverse events should be reported. Indicators of unnecessary or potentially harmful prescribing include duplications such as H2 receptor blockers and proton pump inhibitors and potentially harmful drugs such as long acting hypoglycaemic agents which should no longer be used. The third category of indicator is evidence based. These indicators measure the extent to which research evidence is
MEDICATION REVIEW

Medication review is an essential process in the management of patients with chronic disease. This process should be driven by four questions and should involve the patient as much as possible:

1. Which drugs are necessary for the patient?

The first step should be to look at all the problems and diseases of the patient and to determine which drugs are indicated (32). It is important to identify indicated drugs that are missing. In making decisions, prescribers should consider the remaining life expectancy, goals of care and potential benefits of medications (33).

2. Which drugs are not necessary?

The next step is to look at the medicines the patient uses, including the OTC drugs, and to determine for which drugs there is still an indication. Unnecessary duplications with other drugs should be looked for (e.g., H2 blockers and proton pump inhibitors), taking into account drugs that will be added to the regimen as above.

3. Are there better alternatives for the remaining drugs?

The proposed drugs should be prescribable together. It is important to look at clinically significant drug-drug and drug-disease interactions (34). It is also important to ask the patient about adverse drug reactions and, if so, to look at alternatives. Where drugs have similar efficacy/safety profiles the least expensive option should be prescribed.

4. Is the dose and the dose frequency appropriate?

Consider if the prescribed dose is still correct. Have there been any changes in the clearance of the drug, e.g., a change in renal function?

The patient should always be asked about problems with drug adherence. Adherence can be increased in several ways, but most evidence exists for reduction of the number of daily doses (20).

UNDERTREATMENT

Undertreatment is a common reason for inappropriate prescribing. It has been shown that undertreatment is frequent in elderly patients, despite the use of many medicines (35, 36). Undertreatment in elderly patients is reported in a high percentage of patients with myocardial infarction, chronic heart failure, atrial fibrillation, hyperlipidemia, osteoporosis, COPD, depression, pain and cancer (35–43). Choudhry et al. concluded that a physician’s experience with bleeding events associated with warfarin in patients can cause underprescription of warfarin to other patients (39). Kuzuya et al. showed that the incidence of polypharmacy among frail community-dwelling older people is lower in the oldest members (>85 years) because of underuse of medications for chronic diseases (43). Kuipers et al. found a clear relationship between polypharmacy and underprescription (32). The probability of underprescription increased significantly with the number of medicines (Figure 1.1).

It appears that general practitioners and specialists are not willing to prescribe more drugs to frail old patients with current polypharmacy for reasons of complexity of drug regimens, fear of ADRs, interactions and poor adherence. Research has shown that for some medical problems a so-called treatment-risk paradox or risk-treatment mismatch exists meaning that patients who are at highest risk for complications have the lowest probability to receive the recommended pharmacological treatment (38, 40). The application of clinical practice guidelines...
(CPGs) to the care of older patients with several comorbid diseases may have undesirable effects and there could be reasons not to treat all problems. Moreover, the evidence of the benefit of CPG application in elderly patients with comorbid disease is lacking. Boyd et al. estimated that if the relevant CPGs were followed a hypothetical patient would be prescribed 12 medications (44). However, undertreatment may be harmful for the patient. In optimizing polypharmacy, attention should be directed not only to overtreatment but also to possible undertreatment. The aim is to enhance appropriate prescribing to patients with comorbid diseases. In conclusion, undertreatment is considered an important problem in elderly patients with comorbid diseases although the evidence base is lacking.

REFERENCES


Figure 1.1. Estimated probability of underprescription related to the number of drugs (adapted from Ref (32))


