The problems of drug therapy in the elderly

Problems with drug therapy in the elderly are numerous and drugs often interact in complicated ways. Their causes and how to deal with them are described in detail in later sections but they may be set out under three headings:

the patient

the prescriber

the drugs.

The patient

The main problems from the point of view of the patient may be defined as follows.

Multiple pathology in elderly patients tends to lead to their consuming more drugs than younger patients, with the result that they run a greater risk of developing adverse side effects and drug interactions.

Failure to comply with a drug regimen and errors in administration increase with age. This derives in part from confusion resulting from multiple drug therapy; a bad memory, failing vision and impaired manual dexterity are also important factors. Poor packaging of drugs makes compliance more difficult than it need be. But the most important cause of poor compliance is that patients and their families may fail to understand what they are supposed to do.

Exceptions to normal patterns of drug kinetics and dynamics occur more frequently in old people than in a younger population.

Loss of reserve functional capacity of the heart, liver and kidneys and deterioration of homeostatic control add to the increased vulnerability of old people to drugs.

In old people the outcome of therapy is more likely to be affected by the simultaneous use of old or borrowed drugs, or self-medication with over-the-counter products. .

The prescriber

The principal problem affecting prescribers is that inadequate teaching often leads to ignorance about the many differences between old people and younger people with respect to drug therapy. Part of this ignorance is genuine in the sense that much is not understood, but much is in fact known and not properly applied. Prescribing is always the responsibility of the prescribers and they will best protect themselves by adequate knowledge.

Multiple pathology is so common in the elderly that difficult decisions have to be taken about which condition should be treated first and which should be, perhaps temporarily, left untreated, i.e. an order of priorities must be established. There may also be no drug available for some conditions, and therefore it must be accepted that not all conditions found can be treated with medicines (see Table 1). Multiple pathology is a standing invitation to multiple prescribing, and the problems this raises will be even greater if drugs are given to treat the side effects of other drugs. Simplicity is the most important single principle for prescribers to observe.

Table 1. Drugs of uncertain or no value in the elderly

Drugs claimed to counter mental or physical senility
Drugs with purported aphrodisiac properties
Peripheral and cerebral vasodilators
Expectorants
Analeptics
Anti-obesity drugs

The drugs

Particular problems with the drugs themselves that arise in old age include:

alterations in drug kinetics

alterations in drug dynamics

interactions between drugs (more common the more drugs are taken)

the physiological effects of aging and disease.

Because of such uncertainties, one should generally be cautious of using new drugs in the elderly.

Some of these problems are discussed in more detail in later sections.

How aging may affect drug action

A rational approach to drug therapy in the elderly requires an understanding of the changes in pharmacodynamics (drug response) and pharmacokinetics (drug handling) that are likely to occur in this age group. The two are essentially interrelated since pharmacodynamics, which may in a general sense be determined by the amount of active drug available at the site of action (be it a physiological function or a pathological process), will obviously be influenced by pharmacokinetic changes in the elderly. Alterations in the sensitivity or density of the receptors on which drugs act or in the integrity of the physiological homeostatic mechanisms are further factors that, together with the presence of disease, are likely to influence pharmacodynamics in old age.

As yet it is not possible to separate clearly age effects *per se* from those resulting from aging associated with the presence of disease. It is therefore important to appreciate the large variability in drug response that occurs in a heterogeneous elderly population, ranging from "fit old folk" to the grossly debilitated. The presence of multiple pathology and the consequent need in many cases to prescribe several drugs concurrently adds a further complication. The consequences of alterations in pharmacokinetics or drug sensitivity in the elderly will obviously be more important with those drugs that have a narrow safety margin, such as cardiac glycosides and anticonvulsants.

Pharmacokinetics

Pharmacokinetics may conveniently be considered under the headings of absorption, distribution, hepatic metabolism (including presystemic elimination, i.e. rapid intestinal or hepatic inactivation before the drug reaches the systemic circulation) and renal excretion.

With old age a number of changes occur in the gastrointestinal tract that might be expected to alter drug *absorption*, for example increased gastric pH, decreased intestinal blood flow secondary to decreased cardiac output, and alterations in gastric emptying time and gastrointestinal motility. It is perhaps surprising therefore that, with some notable exceptions such as phenytoin, barbiturates and prazosin, the available evidence indicates that the rate and extent of drug absorption are unchanged in the elderly and that changes, where they do occur, are unlikely to be of clinical significance, particularly during long-term therapy. The increased bioavailability of levodopa and propranolol in some elderly patients results in part from decreased inactivation in the gastrointestinal tract. In the case of levodopa this may influence the therapeutic outcome, at least when the drug is not given together with a decarboxylase inhibitor.

The most important features of a drug's *distribution* relate to that in the body fluids and the extent of binding to plasma proteins (usually to albumin but, with some drugs, to other proteins such as α_1 acid glycoprotein), to red cells and to body tissues, including the target organ. In old age there is a significant decrease in lean body mass and total body water, an increase in body fat (particularly in males) and a small but significant decrease in plasma albumin. While it is difficult to generalize, the distribution volume of water-soluble drugs such as furosemide and paracetamol may decrease in the elderly, while lipid-soluble drugs such as lidocaine, amitriptyline and diazepam appear to be more extensively distributed. Overall, the elderly are smaller in body size than younger people and this may contribute in part, for example, to the higher blood levels of digoxin in the elderly than in the young following the same intravenous dose. The age-related decrease in plasma albumin concentration, which is slight in healthy old people, may be more significant in ill, poorly nourished or severely debilitated old people and will result in an increase in the free, pharmacologically active fraction of some drugs, sometimes

leading to more marked effects but more rapid elimination. The practical significance of such changes in distribution volume and extent of protein binding is unclear, but they are of major importance in the interpretation of other pharmacokinetic data, such as the plasma half-life of drugs. It is doubtful whether changes in protein binding in healthy old people are of clinical importance, although the possibility of such changes influencing, or reflecting an alteration in, a drug's penetration to its site of action cannot be excluded. There is as yet a shortage of information on this, even from animal studies, and it should be realized that subtle changes in drug distribution in the elderly may occur in the absence of any significant alteration in plasma pharmacokinetics.

The onset of drug effect is largely determined by the rate of absorption and manner of distribution. The duration of effect is influenced more by the rate of *elimination*, principally by metabolic degradation in the liver, usually to more polar, less active metabolites or by renal excretion of the parent drug or its metabolites. The hepatic clearance of phenazone (antipyrine), a drug widely used as an index of liver microsomal oxidation, is reduced in the elderly, partly due to an age-related decrease in functional liver volume and partly to a reduced rate of hepatic metabolism. Several other drugs undergoing oxidation exhibit a similar reduction in clearance (e.g. chlordiazepoxide, theophylline) but for some other drugs (e.g. warfarin, diazepam) no age-related differences in clearance exist. It is apparent therefore that there is no simple pattern of age-related change in drug metabolism. Changes, where they occur, are often small and may be less important than those brought about by environmental factors such as cigarette smoking.

A number of drugs are so avidly extracted by the liver, i.e. by uptake into hepatic binding sites and by metabolism, that their clearance depends on the rate of delivery to the liver by the blood. In old age a decrease in hepatic blood flow, together with a possible reduction in the rate of hepatic metabolism, is responsible for the reduced elimination of such high-clearance

drugs as labetalol, lidocaine and propranolol. With such highly cleared drugs there is a marked first-pass effect due to their extensive presystemic removal from the blood on their first passage through the liver. Their oral bioavailability is therefore low but is increased in the elderly due to a reduction in the first-pass extraction.

Drug metabolizing ability may be enhanced by treatment with enzyme-inducing agents such as phenobarbital or phenytoin, or by exposure to environmental factors such as cigarette smoking. There is limited evidence to suggest that the induction response may be reduced in the elderly. If this is the case, the elderly, as well as having a lower baseline ability to metabolize some drugs (e.g. rifampicin, disopyramide) will be less able to develop tolerance to metabolized drugs.

The effects of age on renal function exert a profound influence on the elimination of a number of drugs. In many cases drugs are excreted by simple glomerular filtration, and their rate of excretion correlates with the glomerular filtration rate (and hence with creatinine clearance), for example digoxin and the aminoglycoside antibiotics. In old age renal function diminishes, together with renal blood flow, so that by the age of 65 there is a reduction of approximately 30% in the glomerular filtration rate compared with young adults. The range is wide, however, and many elderly people maintain a perfectly normal glomerular function. Tubular function also deteriorates with age, and drugs such as penicillin and lithium, which are actively secreted by the renal tubules, show a marked reduction in clearance. In addition to physiological decline in glomerular and tubular filtration, the elderly patient is particularly liable to renal impairment due to dehydration, congestive heart failure, hypotension and urinary retention or to intrinsic renal pathology such as diabetic nephropathy or pyelonephritis, which may further modify the renal handling of drugs.

Where there is obvious renal disease, guidance on the appropriate dosage of renally excreted drugs may be obtained from standard tables. Because of diminished muscle mass and lower

protein breakdown, apparently normal blood urea or creatinine values do not preclude a substantial deterioration of kidney function; the renal reserve is smaller in elderly patients than in younger people and therefore the dose of such drugs should always be chosen with this in mind. This is particularly important because of the serious effects of overdosage with some drugs, for example digoxin, lithium and aminoglycoside antibiotics. In general, elderly patients are best treated with lower doses of renally excreted drugs than are younger patients.

Much of the pharmacokinetic data on hepatic metabolism and the renal excretion of drugs in the elderly has been obtained from single-dose studies, and there is a lack of data on age-related comparisons of steady-state drug levels with long-term dosing. With renally excreted drugs such as digoxin, lithium, penicillin and streptomycin, adequate serum levels are obtained in the elderly with lower doses. With metabolized drugs it is again not possible to generalize. Plasma steady-state levels of propranolol and phenytoin increase with age as do those of some, but not all, tricyclic antidepressants.

Receptor sensitivity

Although pharmacokinetic differences can account for many age-related alterations in drug effect, there is still a significant residue of altered responsiveness that seems to be explicable only by a change in tissue sensitivity to drugs. This age-dependent difference in responsiveness is so great with some drugs that the effect may differ from the usual pharmacological spectrum of the drug in question.

Practical and methodological difficulties preclude in almost all cases the true determination of numbers and sensitivity of receptors and, for the most part, the data available simply relate the plasma drug concentration to the pharmacological effect. Using this approach, the elderly central nervous system shows an increased sensitivity to single doses of psychotropic drugs such as morphine, almost all benzodiazepines and most

antipsychotics. Such age-related changes do not result from altered pharmacokinetics, although the possibility of an increased penetration of the drugs into the elderly brain cannot be ruled out. Increased sensitivity to drugs can occur in other systems; for example, coumarin anticoagulants have a greater effect on clotting factor synthesis in the elderly in the absence of changed pharmacokinetics.

The only receptor system for which any appreciable data exist in relation to human aging is the beta-adrenoreceptor. Evidence from studies on the blockade by propranolol of either isoprenaline-induced or exercise-induced tachycardia indicates that both drugs have a reduced effect in the elderly. This would seem from studies on human lymphocytes to be related to a reduction in the number of such receptors or to an alteration in their characteristics in old age.

Drug interactions

Drug interactions stemming from effects on pharmacokinetics, thus altering the amount of drug reaching receptor sites, or from modification of the events at the receptor occur in all age groups. The frequency of their occurrence, however, is directly related to the number of drugs prescribed and for this reason such polypharmacy is particularly hazardous in older patients. In addition this frequently leads to admission to hospital.

Homeostatic mechanisms

Reduction in the efficiency of the homeostatic mechanisms appears to be an integral part of the aging process, with the result that the elderly are less able to compensate for the effects of many drugs and are therefore more vulnerable to their adverse effects.

As a result of impaired baroreceptor function, drug-induced postural hypotension is particularly evident in the elderly. Drugs used in the treatment of hypertension are prominent offenders;

in particular, the thiazide diuretics carry a high risk of postural hypotension, as do a number of psychotropic agents such as the phenothiazines, tricyclic antidepressants, monoamine oxidase inhibitors and antihistamines.

The elderly have a marked reduction in their ability to thermoregulate, and drug-induced hypothermia, resulting from a direct pharmacological effect or indirectly through reduced mobility, is a particular problem associated with old age. The phenothiazines produce particular difficulties in this respect, but barbiturates, benzodiazepines, tricyclic antidepressants, narcotic analgesics and alcohol, alone or in combination with other drugs, may also produce considerable difficulties.

Falls occur frequently in old age as a result of impaired maintenance of posture, and drug-induced increases in the frequency of falls may well result from the effects of drugs on the mechanisms of postural control. Such sudden falls may also be caused by drug-induced arrhythmias. For this reason anti-arrhythmic drugs should be reserved for the treatment of life-threatening arrhythmias.

The maintenance of normal intellectual function, the regulation of blood sugar levels and the neurological control of bladder and bowel function may also be less efficient in old age, leading to increased sensitivity to the pharmacological or adverse effects of a variety of drugs.

Pathology

There are considerable difficulties in attributing age-related alterations in drug response to age *per se* or to age associated with pathological change, and exact comparability of groups is essential in such comparisons. Elderly patients often have multiple pathology, and marked alterations in pharmacodynamics and pharmacokinetics may occur, stemming either directly from the pathology or indirectly from associated complications such as poor nutrition, anaemia, and failure of the hepatic, renal, cardiac or peripheral circulation. The increased risk of haemorrhagic

complications of anticoagulants in the elderly is due, at least in part, to degenerative vascular disease diminishing the haemostatic response. Fortunately knowledge of the effects of disease on drug effects in the elderly is now rapidly improving, and research in this field is expanding.

Choosing the right preparation

Some old people may have difficulty in getting to a pharmacy, perhaps because of distance or infirmity. It is little use prescribing a drug if the prescription is not going to be filled. Sometimes the pharmacy does not stock a particular drug, and it will be useful to ascertain the availability beforehand.

Oral preparations

Containers

Many old people are alert and have clear vision and nimble fingers. They experience no greater difficulty in taking drugs than their younger counterparts. At the opposite end of the spectrum are patients with mental impairment, poor vision, swallowing problems and arthritic hands. Here many obstacles lie between the drug in its container and the target organ in the patient.

Old people often have difficulty in getting drugs out of containers. Medicine bottles should therefore be large enough to be easily handled, have a neck through which tablets and capsules easily flow, and have a top that is easily removed (or replaced) by screw or bayonet action.

Containers in current use often have childproof lids; one old person in ten cannot open these. A much larger proportion can use the container, but experience such difficulty that compliance is seriously reduced. Most patients solve the problem by not closing the lid after use. Childproof containers, then, should be issued to old people only when they are living with young children. In such a case the pharmacist should ensure that either the patient or a relative knows how to operate the container.

Tablets and capsules in bubble packs should not be dispensed to old people; about a third of them do not have the manual dexterity to open these packs. An even greater proportion either crush the tablets or drop them on the floor when using bubble packs.

Attempts have been made to improve compliance by placing drugs in dispensers with compartments labelled with dates and times. These are rarely successful with old people, who often cannot get their fingers into the compartments or turn the dispenser upside down so that all the tablets fall out. Bubble packs labelled with dates and times have also been prepared for individual patients; if patients understand their use, these can occasionally be quite practical.

Cost

The prescriber should consider the cost of the course of treatment, especially where elderly patients will have to pay for the drugs themselves.

Information

Containers should be labelled with lettering clear enough to be seen by patients with failing vision. Important information comprises the names of the prescriber and patient, the name of the drug, the method and frequency of dosage, and the condition for which it is prescribed. Vague instructions such as "as directed" should be avoided. The label should also give the name of the pharmacist, the date of dispensing and the date of expiry. Such information reduces the risk of one spouse taking the other's tablets, or an old person hoarding a medicine and using it long after expiry of its shelf life. About 25% of elderly patients are not able to remember what the purpose of the drug was.

Tablets and capsules are more easily identified if they are in a container made from clear glass. Dark glass should be used only if light is likely to have a serious effect on the stability of the preparation.

Doctors and pharmacists should also ensure that, after a patient has been discharged from hospital, the local pharmacist dispenses tablets with the same size, shape and colour as those used previously. The patient will also be confused if the name of the drug is changed from a generic to a proprietary one or vice versa. Such confusion is often difficult to avoid when the patient is moved from home to hospital or vice versa. The increasing use of generic drugs and the avoidance of colouring matter often lead to the pharmacist's handing out round white tablets of almost uniform size, and this may bewilder many old people.

Size, shape, colour and appearance of tablets and capsules

Old people have difficulty in swallowing large tablets, particularly if they have a dry mouth or a bulbar or pseudobulbar palsy. Conversely, patients with poor eyesight or arthritic hands may have difficulty in coping with small tablets. Each patient, then, requires individual assessment. In addition to not working, an unchewed tablet may cause local irritation; old aspirin tablets, for example, may cause unpleasant mouth ulcers in old people.

Consideration should also be given to the rate at which tablets travel down the oesophagus. Abnormal motility patterns may lead to considerable delay in old people. The dissolving of irritant tablets in the oesophagus accounts in part for the high incidence of gastrointestinal disturbances associated with medication in the elderly. Drugs causing this include doxycycline, non-steroidal anti-inflammatory agents (including aspirin), iron salts and some anticholinergic drugs. General rules for reducing the problem are that tablets will move more rapidly if they are small, of high density and oval rather than round. Again, tablets are less prone to stick than capsules, and should be prescribed in preference if there is a choice. Rapid transit is also more likely if the patient stands (or sits up in bed) and for the same reason it is strongly recommended that the patient drink at least 100 ml of water with the medicine.

Patients sometimes have prejudices against particular colours. Some, for example, associate green with poisons; others feel that red tablets are particularly dangerous. Such fears can often be allayed by explanation.

The prescription of capsules to an elderly patient accustomed to tablets may cause misunderstanding; a patient may, for example, attempt to empty ampicillin out of its capsule before taking it. Moreover, some effervescent formulations may be swallowed dry instead of dissolved in water.

Size of dose

Age-related changes in the metabolism and excretion of a drug or its end organ responsiveness often mean that old people require much smaller doses. An example is nitrazepam, for which the dose recommended for elderly patients is 2.5–5 mg at night. They may be advised to take only half-tablets, but this is often easier said than done by a patient with failing eyesight and arthritic hands. There are advantages, therefore, in prescribing tablets that contain small doses. Examples include 62.5-mg capsules of levodopa with benserazide, 0.0625-mg tablets of digoxin and 12.5-mg tablets of hydrochlorothiazide.

Frequency of dose

Compliance is improved by prescribing a drug that can be taken once or twice rather than several times a day. Whether this is practicable for a given preparation will depend on its duration of action. One way of prolonging this is to dispense drugs in slow-release capsules. In young people this can often be relied on to prolong the duration of action to 12 hours. In old people the effect may be less predictable.

An alternative is to use a drug that is slowly excreted or metabolized. Reduced renal and hepatic function, however, can lead to cumulation and toxicity from some such drugs in old age. An example is the long-acting non-steroidal anti-inflammatory drug

piroxicam, which is more prone to cause gastric ulcers and haemorrhage in old people. Short-acting drugs such as ibuprofen, given several times per day, may be much safer.

There are many drugs for which a sustained clinical effect does not depend on maintaining a high blood concentration. This means that, although they may have a relatively short plasma half-life, single daily doses are all that may be required. Examples include tricyclic antidepressants given as a single evening dose, thioridazine or chlorpromazine given as a single evening dose, and corticosteroids given every second day. This approach is practicable only when relatively small doses are given. For example, if more than 75 mg of thioridazine is required, it should be given in divided doses.

Exceptions to the rule that doses several times a day should be avoided include drugs used in Parkinson's disease; doses of levodopa may have to be given up to two-hourly to avoid the "on-off" pattern that often develops in more advanced disease.

Liquids

If patients have difficulty in swallowing tablets and capsules, then elixirs, mixtures, solutions, tinctures and syrups may be useful alternatives. There are also patients who derive greater psychological benefit from taking a brightly coloured bitter liquid rather than a white tasteless pill. Finally, drugs in liquid form can be mixed with food; for example an agitated, uncooperative and suspicious old person can be given haloperidol drops in tea or soup.

A limitation of liquids is that it is very much more difficult to give accurate doses. Patients may use the wrong size of spoon. Even if they use a standard plastic spoon they have to pour from a bottle, fill the spoon to the brim, and move the spoon up to their lips. This operation becomes difficult if the patient has poor vision, arthritis or a tremor. These problems can be partially resolved by issuing graduated plastic beakers.

Parenteral preparations

A major advantage of parenteral preparations over oral ones is that compliance is ensured. It is easier to maintain vitamin D levels with injections of 600 000 i.u. of ergocalciferol every 6 months than to persuade a patient to take 500 i.u. daily as tablets of calcium and vitamin D. Again, it may be easier to control agitation in an uncooperative patient with intramuscular injections of 25 mg of fluphenazine decanoate every 3 weeks than with a comparable neuroleptic given orally.

A disadvantage of long-acting parenteral injections is that, if there are side effects, they may take a long time to disappear. Hypercalcaemia from vitamin D intoxication persists for weeks, and oversedation from injected phenothiazine esters persists for days.

Intramuscular injections may also be extremely painful. Penicillin G, chlorpromazine and aminophylline are all extremely irritant. Intramuscular injections of iron are particularly unpleasant and should never be used if intravenous preparations are available; if compliance is poor and correction of iron deficiency important, the mineral should be given intravenously. Some drugs that act when given intravenously are ineffective by the intramuscular route.

If a patient is living at home, injections may have to be given by a relative or a community nurse. This is not always a disadvantage. Monthly injections of vitamin B_{12} may, for example, give a community nurse a reason for looking in to see how a frail old person is coping alone.

In many countries, however, it is a common but misguided belief that drugs given parenterally are more effective than those given by any other route. This superstition should be challenged. Moreover, disposable syringes and needles are expensive and under unhygienic circumstances may contribute to the spread of HIV and hepatitis infection.

Other routes

Suppositories

Emaciated old people have little gluteal muscle left for intramuscular injections. Even where this is not the case, patients with nausea or acute pain may find repeated painful injections unacceptable. In such situations, drugs may be given *per rectum*. Preparations given by this route include antihaemorrhoidal preparations, ergometrine, indomethacine, mesalazine, metronidazole, chlorpromazine and paracetamol. Aminophylline suppositories still enjoy great popularity, but their use should be discouraged because theophylline absorption from this formulation is low and unpredictable.

When rapid action is required and the drug cannot be administered in any other way, it may be given rectally in liquid form, such as small enemas of corticosteroids in ulcerative colitis or diazepam in status epilepticus.

Inhalations

A wide range of drugs used in chronic airflow limitation are available as aerosol or microcrystalline powder inhalations. The patient must be carefully instructed in their proper use. Many old people have neither the mental function, the manual dexterity nor the respiratory coordination to cope with them. One approach to the problem is to attach the insufflator to an expanded airway. If the drug is insufflated into this it remains there for some time so that the timing of inspiration by the patient becomes less crucial. The diversity of design shows that the ideal solution has not yet been found, and further experience is required to see whether this approach is useful in old people.

Combination products

One way of simplifying medication and thus improving compliance is to combine different substances in one tablet.

Examples include beta-blocking agents combined with thiazide diuretics, thiazide diuretics combined with potassium-sparing agents, and tricyclic antidepressants combined with phenothiazine tranquillizers. These should only be used if one drug is inadequate. For example, moderate hypertension should be treated initially with either a thiazide diuretic or a beta-blocking agent and the other drug added only if the first is ineffective. Combination drugs, again, do not absolve the clinician from the responsibility of careful monitoring. Patients on thiazides and potassium-sparing agents may still become hypokalaemic or hyperkalaemic. A further problem is that, with combination products, it is impossible to tailor drug ratios to individual requirements. Economic considerations should not be allowed to override these principles.

Alternatives to drugs

Patients not keen to take vitamins or minerals as tablets or medicines can sometimes be persuaded to take them as supplements to their diet. For example, orange juice contains high concentrations of ascorbic acid, and orange juice or tomato juice high concentrations of potassium. Many fresh vegetables contain such ingredients, which may be destroyed by overcooking.

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Adverse drug reactions in the elderly

An adverse drug reaction (ADR) is any harmful or unwanted effect caused by a drug taken as instructed in its regular dosage.

Old people are at particular risk of developing ADRs. To some extent this is due to the mere fact that old people in general take more drugs than the young. To this must be added the fact that elderly patients, owing to pharmacodynamic and pharmacokinetic changes as well as loss of reserve capacity and reduced homeostatic control, are more sensitive to the harmful effects of drugs. Poor compliance, being more common in old age, is another cause of side effects. So is multiple medication; one community study showed that the prevalence of side effects was 18% in those using fewer than 6 drugs and 80% in those using more than 6 drugs.

ADRs in elderly patients contribute to morbidity and not infrequently result in the patient's deciding to withdraw from the treatment. Some 10–20% of patients admitted to geriatric departments suffer from side effects, and in 5–12% of such cases these were the main reason for admission. In this context, the most frequent causative drugs are diuretics, psychotropic drugs of all types, digitalis glycosides, non-steroidal anti-inflammatory agents (including aspirin) and antiparkinson drugs.

ADRs are frequently overlooked in the elderly. One main reason is that doctors tend to forget that virtually any symptom in an old person may be drug-induced or aggravated by drug treatment. The other is that, as a general rule, the diagnosis of ADRs is difficult, and perhaps especially so in the elderly.

The diagnosis of an ADR is based primarily on a meticulous drug history, the establishing of a temporal relationship between exposure to the drug and the clinical manifestations, and improvement on withdrawal or dosage reduction. Most

doctors have experienced the often insuperable problem of getting a precise drug history from an old person living alone. The best way of ensuring that reliable information is obtained is probably by making a home visit to see all the patient's drugs. As a general rule patients should bring all their drugs with them whenever they enter hospital.

ADRs in the elderly often occur during the first 1–2 weeks after starting treatment or increasing the dose. There are, however, important exceptions to this generalization, such as disturbances of serum potassium due to diuretics, tardive dyskinesias after prolonged use of antipsychotic drugs, and acute leukaemia due to alkylating cytotoxics given many years earlier. Severe ADRs in the elderly are, in 9 out of 10 cases, due to a drug's well known pharmacological effects, and are not infrequently precipitated by drug interaction. Allergic reactions, most commonly caused by antimicrobial drugs (e.g. ampicillin derivatives, sulfonamides) seldom give rise to therapeutic problems in the elderly. Allergic reactions can, however, produce difficult diagnostic problems if the patient presents with fever (drug fever) as the principal manifestation.

Abrupt withdrawal of certain drugs (benzodiazepines, beta-blockers) can cause severe reactions in the elderly.

Rechallenge is the most powerful diagnostic tool when a side effect is suspected. Severe and even fatal reactions can result from such experimentation, however, and rechallenge should for obvious ethical reasons be left to experts.

Geriatric practice is often complicated by the nonspecific symptomatology of disease in old age, the patient or the family characterizing the major symptoms as lassitude, weight loss, lightheadedness, urinary incontinence or confusion. All these symptoms can be drug-induced, and some frequent offenders are listed in Table 2.

Another complicating factor in geriatric medicine is that severe disorders so often start insidiously and are therefore easily overlooked by the patient as well as by relatives and the doctor. The most frequently overlooked disorders in the elderly

Table 2. Drugs regularly detected as the culprit in some common disorders of the elderly

Confusional states	Depression	Falls	Postural hypotension	Constipation	Urinary incontinence	Parkinsonism
hypnotics	methyldopa	hypnotics	all anti-hypertensives	codeine	loop diuretics	antipsychotics
tranquillizers	reserpine	tranquillizers	diuretics	dextro-propoxyphene	hypnotics	drugs for vertigo
antidepressants	beta-blockers	antidepressants	anti-anginal drugs	narcotic analgesics	tranquillizers	methyldopa
antipsychotics	tranquillizers	antipsychotics	beta-blockers	diuretics	antipsychotics	reserpine
anticholinergics (centrally acting)	levodopa	antihistamines	hypnotics	anticholinergics	prazosin	metoclopramide
non-steroidal anti-inflammatory drugs	corticosteroids	carbamazepine	tranquillizers	disopyramide	labetalol	
levodopa		phenytoin	antidepressants	verapamil	urapidil	
bromocriptine		glyceryl trinitrate	antipsychotics	nifedipine	beta-blockers	
antidiabetics (hypoglycaemia)		all drugs liable to produce postural hypotension	antihistamines	antipsychotics	lithium[a]	
corticosteroids			levodopa	antidepressants	all drugs liable to produce faecal impaction	
digitalis glycosides						
anticonvulsants						
cimetidine						

[a] Because of polyuria.

tend to be depression, cognitive defects (e.g. dementia) and parkinsonism, which can all be precipitated or aggravated by drugs (Table 2).

The best way of treating any patient with a suspected ADR is by drug withdrawal or dosage reduction under clinical surveillance. In some cases, where the patient deteriorates when the dose is reduced, it may be appropriate to prescribe an additional drug to control the side effects, such as potassium supplements for hypokalaemia caused by a diuretic, or anticholinergics for drug-induced parkinsonism. The widespread use of anticholinergic drugs to prevent neuroleptic-induced dyskinesias should be condoned, however, because further deterioration of symptoms is not uncommon. Minor complaints caused by side effects, such as dry mouth or slight palpitations during treatment with a tricyclic antidepressant, are usually no reason for withholding therapy and are normally easily handled by reassuring the patient. Quite often, the history and clinical examination of patients with side effects reveal that no valid indication for the offending drug has been present. A typical example is when an elderly patient develops parkinsonism that proves to be caused by the neuroleptic prochlorperazine given for dizziness, which turns out to be due to postural hypotension. In cases like this, diagnosing and treating an ADR by withdrawing a harmful and inappropriate drug are especially rewarding.

ADRs can to a large extent be avoided in the elderly by choosing safe and effective drugs and applying sound therapeutic principles in prescribing, such as starting with a small dose, observing the patient frequently and avoiding excessive polypharmacy.

Some drugs, such as barbiturates, should not be used at all in the elderly as they cause a lot of problems and are easily replaced by safer alternatives. Many drugs are hazardous for the long-term treatment of old people due to their low margin of safety (low therapeutic index) or because their elimination is either so slow that accumulation is most probable or is dependent on kidney function, which is so frequently reduced in the elderly. Examples of such drugs include the aminoglycoside antibiotics

for systemic use, amiodarone, chlorpropamide, digoxin, metformin, lithium, nitrofurantoin and perhexiline maleate. Table 3 lists some drugs with potentially severe or unusual side effects in old people.

Table 3. Drugs with potentially severe or unusual side effects in the elderly

Drug	Unwanted effect
aminoglycoside antibiotics	deafness, renal failure
all barbiturates[a]	confusion
anticholinergic drugs (centrally acting) e.g. trihexyphenidyl	visual and auditory hallucinations
cardiac glycosides	behavioural disorders, abdominal pain, fatigue, anorexia and weight loss, rhythm disorders
chlorpromazine	postural hypotension, hypothermia
co-trimoxazole	agranulocytosis, aplastic anaemia, serious skin reactions
disopyramide	urinary retention, constipation
enalapril (captopril) in cardiac failure	renal failure, first-dose hypotension
estrogens	fluid retention, congestive cardiac failure
flunarizine, cinnarizine	parkinsonism
furosemide	hypotension, cerebrovascular accidents
isoniazid	hepatotoxicity
lithium[a]	urinary incontinence, dehydration[b]
mefenamic acid	diarrhoea, liver damage
methyldopa	drowsiness and depression
nitrofurantoin[a]	peripheral neuropathy, lung reactions
non-steroidal anti-inflammatory drugs (some) e.g. azopropazone, ketoprofen, piroxicam[a]	gastrointestinal ulceration, haemorrhage and perforation
pentazocine[a]	confusion, variable efficacy
triazolam	confusion, psychotic reactions

[a] Drugs to be avoided in the elderly if possible.

[b] Because of polyuria.

Determinations of serum concentration, where available, have become a valuable tool in geriatric practice, where they serve as an adjunct both in the diagnosis of ADRs and undertreatment and in the routine surveillance of asymptomatic patients. Unfortunately, hypoproteinaemia and hypoalbuminaemia are common in sick old people, obscuring the interpretation of such data for highly protein-bound drugs. It may seem prudent, therefore, to aim initially at the lower half of the recommended therapeutic concentration range when titrating doses for the elderly according to serum concentrations. Drugs for which routine determinations of serum concentrations may be appropriate for the prophylaxis of side effects in the elderly are listed in Table 4.

Table 4. Drugs for which routine determinations of serum concentrations may be appropriate to avoid adverse drug reactions in the elderly[a]

aminoglycoside antibiotics (systemic use)
anti-epileptic drugs
digitoxin
digoxin
disopyramide
lithium
theophylline

[a] Routine determination of serum concentrations must be performed in samples drawn at a standardized time after the last dose.

The establishment of the proper use and the safety of new drugs depends to a large extent on the spontaneous reporting by doctors of cases of suspected side effects. Life-threatening and unusual reactions believed to be caused by newly released drugs should always be reported to the national adverse drug reaction centre. Early recognition of some very typical disease entities as drug-induced may save lives. Life-threatening or unusual, possibly drug-induced disease entities include:

agranulocytosis

aplastic anaemia

anaphylactic shock

angioedema

Lyell's syndrome (toxic epidermal necrolysis, exfoliative dermatitis)

Stevens-Johnson syndrome (erythema multiforme)

acute severe hepatitis

lactic acidosis (anion gap)

atypical ventricular tachycardia ("torsade de pointes") often preceded by prolongation of the corrected Q-T interval on the electrocardiogram (ECG).