Today's Treatment

Clinical pharmacology

Drugs and the elderly

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The risk of adverse reactions overshadows all other considerations when prescribing for the elderly, although there is some suggestion that general practitioners, who are responsible for the bulk of prescribing, may not be fully aware of this.¹ Elderly patients are more likely than the young to react adversely to drugs prescribed in hospital,² and they are also more likely to be admitted to hospital³ or to die⁴ because of adverse reactions. Note, however, that such studies do not display the other side of the coin—the benefits of drug treatment—nor can we assume that all adverse reactions are preventable. If the elderly have a genuine need for more drugs than the young, as seems probable, they will inevitably pay some price for effective treatment, even if prescribing was beyond reproach. In fact, most doctors will admit that prescribing (particularly that of other doctors) is less than perfect, and we should aim at reducing adverse effects in the elderly to the minimum while avoiding a harmful degree of nihilism.

The high incidence of adverse reactions in the elderly has two distinct components, each with its own remedy. One relates to the pattern of prescribing in the elderly, and might yield to changes in prescribing habits. The other reflects the propensity of older patients to react adversely to certain individual drugs, and might be countered by more informed use of these drugs.

Prescribing in the elderly

The elderly receive more drugs than the young. While those aged over 65 make up 12% of the population they account for 33% of the national expenditure on drugs.⁵ In one general practice 87% of those aged 75 or over were having regular drug treatment, and no fewer than 44% were taking three or more drugs regularly.⁶ In addition many of the conditions more prevalent in the elderly, such as heart failure and Parkinsonism, need treatment with drugs that have a narrow margin between therapeutic and toxic doses. On the other hand, the use of some drugs with a more favourable therapeutic ratio—for example, those for skin diseases—does not increase with age.⁷ Thus the elderly receive more drugs, and are more likely to receive relatively toxic drugs, and this is entirely to be expected from the pattern of illness in the community. What is not known is how much of this prescribing is unnecessary, ineffective, or inappropriate. Indeed, we may never know, because the topic is

extremely subjective and sensitive.¹ We suspect, however, that adverse effects in the elderly could be reduced considerably, without loss of therapeutic benefit, by a concerted effort to prescribe only drugs that are necessary and have proved to be effective and by a shift from relatively toxic drugs to safer alternatives. It is encouraging to note the large fall in the prescribing of barbiturates that resulted from just such a policy.

The polypharmacy that prevails in the elderly has further important consequences. *Drug interactions* are more likely, and can be avoided only by constant vigilance. Ideally all prescribing should be in the hands of a single doctor. If not, it is important for all communications between hospital and general practitioner (in either direction) to include a complete list of the drugs and doses prescribed. Comments from hospital doctors on *repeat prescribing*, and on the writing of prescriptions by ancillary staff, are seldom welcome, and these aspects are under examination within general practice.¹ As many as half of those aged over 70 obtain drugs on repeat prescriptions.⁷ Cardiovascular and psychotropic drugs figure prominently in these scripts,⁷ and are also important causes of adverse reactions in the elderly. Finally, *non-compliance* deserves mention, although cynics may argue that it is more often a protection against adverse reactions than the cause. Non-compliance is not a problem confined to the elderly,⁸ but it tends to increase with the number of drugs (and doses) given, and treatment errors are certainly common. In one study half of the elderly patients discharged from hospital had deviated from their recommended treatment within 10 days.⁹ Poor understanding seems more of a problem than deliberate non-compliance, and most readers will be familiar with the "Nitrazepam (Mogadon) 5 mg in the morning and Bendrofluazide (Neo-nallex) 5 mg at bedtime" type of mistake. Adherence to treatment can be helped by simple clear instructions, in writing if necessary, and by simplifying the regimen, and will certainly not be good if the patient cannot read the label, open the container, or swallow the tablets. Tear-off calendars or tablet identification cards can reduce mistakes¹⁰ but are not widely used so far as we know. Compliance can be checked easily by a surprise raid on the medicine cupboard during a home visit. Supervision of treatment should be arranged if all else fails.

Increased adverse reaction rate to individual drugs

The elderly are more likely to react adversely to a given dose of some drugs but not to others. Reports from the Boston Collaborative Drug Surveillance Program have shown that older patients react significantly more often to nitrazepam,¹¹ flurazepam,¹² diazepam,¹³ chlorthalidone,¹³ heparin,¹⁴ and potassium chloride¹⁵ but not to several other drugs including theophylline,¹⁶

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frusemide,¹⁷ and methyl dopa.¹⁸ The possible causes for increased susceptibility of the elderly to certain drugs are as follows.

ALTERED PHARMACOKINETICS

Current knowledge is summarised in table I, and was detailed in recent reviews.^{19 20} As regards clinical relevance the important distinction is between those drugs eliminated largely by renal clearance and those that are metabolised. Renal function declines

TABLE I—Changes in pharmacokinetics in the elderly

Absorption	Unaltered
Distribution	
Body weight ↓	Increased dose per unit body weight
Body water ↓	Water soluble drugs have higher blood levels, lower distribution volume; lipid soluble drugs have lower blood levels, higher distribution volume
Body fat ↑	Protein binding reduced (phenylbutazone, tolbutamide) or unaltered (diazepam, salicylate)
Plasma albumin ↓	
Metabolism	
Oxidation	Reduced for some drugs (chlormethiazole, phenylbutazone) but not others (diazepam, warfarin). "First pass" metabolism of chlormethiazole, propranolol reduced
Hydrolysis	
Reduction	Unaltered so far as is known
Conjugation	
Renal clearance	Glomerular filtration/tubular secretion decline with age
Environmental factors	Reduced induction of hepatic microsomal enzymes. Enzymes may also be "resistant" to induction
Smoking ↓	
Caffeine ↓	
Alcohol ↓	
Altered diet	

ALTERED PHARMACODYNAMICS

It has been difficult to prove altered "sensitivity" of the elderly to a given concentration of drug at receptor sites, but there is now evidence that this is so for three drugs. Enhanced sensitivity to nitrazepam²² and warfarin²³ is the probable reason for their increased toxicity (or reduced dose requirement) in the elderly. On the other hand, older patients are *less* sensitive to β -adrenergic blockers at the cellular level,²⁴ and they also have a smaller antihypertensive response than the young to β -blockers.²⁵

Impaired homeostasis is generally accepted as one reason why many drugs cause or worsen confusion, postural hypotension, hypothermia, or falls in the elderly. These phenomena have received little formal study, and the line between aging per se and early disease is not easily drawn.

Multiple disease states are common, and it is all too easy to overlook an important contraindication to a drug even when it has been documented before. Diagnoses get "lost" remarkably often in hospital notes and, we suspect, in general practitioners' records. The use of a comprehensive problem list, easily checked when a new drug is prescribed, has much to commend it. Inclusion in the list of previous adverse reactions should prevent the unforgivable error of causing the same side effect twice.

TABLE II—Drugs known to be common or serious causes of adverse reactions in the elderly

Drug	Problem	Action
Benzodiazepines	Daytime drowsiness	Half dose
Tricyclic antidepressants	Drowsiness, postural hypotension, anticholinergic	Half dose
Phenothiazines*	Extrapyramidal reactions	Avoid if possible
Digoxin	Reduced clearance	Reduce dose; rarely needed in sinus rhythm
Phenylbutazone	Increase in all reactions, and in marrow aplasia	Short courses only; choose safer alternative
Tetracyclines**	Renal failure	Consider alternative
Antihypertensive drugs	Postural hypotension	Avoid bethanidine, guanethidine, debrisoquine
Anti-Parkinsonism drugs	Confusion, postural hypotension, anticholinergic	Consider hospital supervision
Oral hypoglycaemics	Nocturnal hypoglycaemia	Choose short-acting drug
Thyroxine	Myocardial ischaemia	Consider hospital supervision
Barbiturates	Many	Do not use
Opiates	Increased sensitivity	Reduce dose
Warfarin	Increased sensitivity	Reduce dose
Heparin	Bleeding	Use for 48 h only

*In addition to well-recognised drugs (chlorpromazine, promazine, thioridazine) phenothiazines are used for vertigo (for instance, prochlorperazine, Stemetil) and in combinations (for instance, fluphenazine in Motipress, Motival).

**Doxycycline does not appear to worsen renal failure.

linearly from the age of 30, and the clearance of drugs eliminated largely by the kidney, whether by filtration or tubular secretion, is reduced to an important degree in old age. This matters little if the drug has a wide margin between therapeutic and toxic doses (penicillin, for example), but the elderly are distinctly at risk from the accumulation of drugs such as digoxin, lithium, and gentamicin, unless the dose is lowered. The serum creatinine concentration is not an accurate reflection of renal function in the elderly, as creatinine production falls with age. Creatinine clearance must either be measured directly or be estimated from a nomogram using age, sex, body weight, and serum creatinine concentration.²¹

The pharmacokinetics of some drugs that are metabolised are altered in the elderly (table I), but unfortunately the main pattern to date has been one of inconsistency. The everyday observation that some 80 year olds are "good" and some 60 year olds "old" reflects a difference between biological and chronological aging, and this makes the elderly a remarkably heterogeneous group to study. In addition, the effects of aging per se have not been separated satisfactorily from environmental

Safe prescribing in the elderly

In table II we make specific recommendations for several drugs, singled out because they are common or serious offenders in the elderly. Apart from this we can only reiterate some of the principles of sound prescribing, because they are particularly important to the elderly. Consider whether a drug is really needed, stick to drugs of proved efficacy, and be sceptical about new drugs. Check whether your chosen drug causes problems in the elderly, and use a safer alternative when possible. Check specifically for contraindications and potential interactions, and double check when using a combination product. Simplify treatment, and be sure that the patient understands it. Monitor the response, be alert to possible side effects, and discontinue the drug as soon as possible. Finally, and most important, always err on the side of *low doses* in the elderly.

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MATERIA NON MEDICA

Mummies, spiders, and pathogens

The church of St Michan's in Dublin is of special interest to doctors, music lovers, and literary historians. The organ is the original one erected in 1724 and tradition has it that Handel played part of the music for the *Messiah* on it. In front of the organ there is a wonderful carving of 17 musical instruments from a single piece of wood. The carving cost £8 in 1724, whereas the organ cost £850. It is the last organ of its type in Ireland still in its original setting.

Once you have toured the inside of the church, the guide takes you outside and unlocks several iron covers which slope against the side of the church at the base of the wall. The visitor descends steep steps to the vaults underneath the church. The Stoker family vault is here, and Bram Stoker is reputed to have written some chapters of *Dracula* after a visit to this vault.

The limestone rock strata in which the crypt is built has a peculiar drying effect. It is at a constant 52°F, and bodies contained in the coffins within the crypt are in a perfect state of preservation, apart from two exceptions. These are the bodies of the Sheares brothers—two Irish patriots—which were lodged here in 1798 after they had been hanged, drawn, and quartered. In 1898, to commemorate the 100th anniversary of the patriots' deaths, a bunch of flowers was brought in and laid on their coffins. Within a short time the patriots' coffins and their contents began to decompose. The guide explains that "infection" was probably introduced by the flowers, though a more probable explanation is that the water in the vase contained bacteria.

Returning to the open air, the guide leads you to a similar iron trap-door set against the wall of the church and takes you down into a further long passage with burial chambers full of coffins. Most of the coffins are well preserved, despite being several hundred years old. Some coffins look as though they have been brought down within the last month. In one of the vaults the coffin lids are missing and the mummified bodies are clearly seen. Their features can be made out, the nails are still on the fingers and toes, and we were assured most joints were still movable. Tradition has it that the mummy furthest from the door is that of a Crusader who will bring good luck to all who shake hands with him. The mummified skin of his right hand has become polished over the years with constant hand shaking. He must have been nearly 7ft tall and his legs had been broken to make his body fit the coffin. In a second coffin is a convicted felon. He has had his right hand chopped off (shades of Islam) and both feet, but there is no record of the crime committed.

Many spiders' webs are present in the vaults, though there is no evidence of flies or other insects. The suggestion is that the only food available for the spiders is one another (cannibalism). This seems a typically Irish solution to the problem, but what do the smallest

spiders feed on? These vaults contain three major scientific mysteries. Firstly, how is the temperature maintained at 52° and the air so dry that mummification occurs, when the church was built on formerly marshy ground within a few hundred yards of the River Liffey? The director of the National Museum of Ireland postulated in 1964 that the mummification was due to the relatively high methane content of the air in the vaults. The second mystery concerns the spiders. A possible explanation is that new arrivals keep coming in from the outside, attracted by the warmth and thus maintaining the numbers. The third mystery is the "infection" that rotted the wood of the coffins and decomposed the bodies of the two Irish patriots. One explanation is that fungal spores or wood-loving bacteria were introduced either on the flowers or in the vase of water.—J M DUNLOP (community physician, Hull).

Penny loaves

On one's way home from school in the 1950s it was common practice to buy a penny loaf. Perhaps the appeal of the miniature had something to do with it, apart from the need to stave off pangs of adolescent hunger. Anxious to do something for the local church bazaar, and being fond of home baking, I called at the local ironmonger to buy a "penny loaf tin." Oh yes, he knew just what I meant, and had himself enjoyed penny loaves as a schoolboy, but no, he had not seen a tin for many years, and certainly had none in stock. Nor apparently had anyone else for 20 miles around. I wrote to a well-known bread company, who used to make loaves with their name in relief on the side; they advised me of shops where I could possibly buy the loaves (not that I have ever seen any in recent years), but they regretted they could not supply the tins. A little daunted I tried the Yellow Pages for bakery equipment manufacturers. I wrote to a random three.

Some months later, one firm replied to say they had found one tin in an old warehouse; they would clean it up, and send it to me with their compliments. It duly arrived; I was delighted and wrote suggesting they make some more for me. Again no reply, and I had forgotten all about it, until driving in after surgery one evening I was in time to see a sports car just about to leave. The driver told me he was a salesman from the firm and had just left something for me in the letter box—with his managing director's compliments. There were 21 penny-loaf tins, fastened together in three serried ranks of seven. Penny loaves have emerged once more at our church bazaar—highly nutritious, homemade, and cheap at three new pence each.—SELWYN H GOODACRE (general practitioner, Swadlincote, Staffordshire).