DOI:10.1111/j.1365-2125.2004.02228.x

Drug development and use in the elderly: search for the right dose and dosing regimen

Rashmi R. Shah
Medicines and Healthcare products Regulatory Agency, Market Towers, 1 Nine Elms Lane, Vauxhall, London, UK

Correspondence
Dr Rashmi R. Shah, Senior Clinical Assessor, Medicines and Healthcare products Regulatory Agency, Market Towers, 1 Nine Elms Lane, Vauxhall, London, UK.
Tel: + 44 20 7084 2349
Fax: + 44 20 7084 2323
E-mail: rashmi.shah@mhra.gsi.gov.uk

The views expressed in this paper are those of the author and do not necessarily reflect the views or opinions of the MHRA, other regulatory authorities or any of their advisory bodies.

Received
29 March 2004
Accepted
20 July 2004

Across the globe over the last few decades, there has been a remarkable increase in the proportion of the population which is elderly, and this trend is set to continue. Data from 10 countries that accounted for about 55% of the world population of 6079 million in the year 2000 provide an overview of this significant shift in demography. Table 1 summarizes the projections for the next 25 years. Hitherto, increases in life expectancy have been most obvious in the affluent countries; however, improvements in public health and disease control are also leading to increases in life expectancy in the less affluent countries. As a result of relatively larger increases in life expectancy at birth, significant shifts in demography are also expected in countries that are at present economically less affluent. The number of elderly people in the world is therefore expected to continue to increase for some considerable time. Interestingly, the most dramatic increases in the proportion of the population who are elderly are anticipated in countries where total populations are projected to decrease (such as Japan, Germany and Italy).

The 2001 population census of the UK revealed that since the census of 1951, the proportion of elderly population above 65 years and 85 years has increased from 16% and 0.4% respectively to 21% and 1.9%, respectively. These changes in demography will have significant effects on the economics generally as well as on the provisions for healthcare. Cardiovascular and neurological diseases and cancers are the most prevalent in the elderly. These three groups of diseases account for about 54% of the total burden of disease in Europe in terms of disability adjusted life years. Of the total gross Hospital and Community Health Services expenditure of £31.9 billion in the year 2001–2002 in the UK, 13% was expended on people aged 65–74 years, 16% on those aged 75–84 years and 10% for people aged 85 years or more. Furthermore, about 55% of the community prescriptions during 2001 in the UK were dispensed for the elderly. Cardiovascular and psychoactive drugs accounted for more than 40% of these prescriptions. In view of many age-related changes in the pharmacokinetics and pharmacodynamics of a drug, the safe and effective prescribing of medicines in the elderly will continue to present a major challenge.

This review provides an overview of the issues relevant to development and clinical use of drugs in the elderly population, with particular reference to determining the right dosage and dose regimen and the regulatory requirements that facilitate this process. It also examines whether, as a result of advancing age per se, the dosing regimens in the elderly and the frail elderly might be different from those in the non-elderly.

Table 1
Age-related demography in 2000 and projected changes in 10 major countries

	2000				Projections for 2025			
Country	Population (millions)	Life expectancy at birth (years)	Total above 80 years of age (%)	Actual number of centenarians	Population (millions)	Life expectancy at birth (years)	Total above 80 years of age (%)	Actual number of centenarians
USA	282	76.6	3.3	51 000	350	80.5	4.5	327 000
Japan	127	80.6	3.8	12 000	120	82.8	9.7	176 000
Germany	82	78.1	3.7	7 000	81	81.2	7.8	76 000
UK	60	77.8	4.0	10 000	64	81.1	5.6	56 000
France	59	78.8	3.7	8 000	63	81.8	6.1	69 000
Italy	58	79.1	4.0	5 000	56	81.9	7.9	73 000
China	1269	71.4	0.9	9 000	1453	77.4	2.3	128 000
India	1002	62.5	0.6		1362	70.9	1.2	
Indonesia	224	68.0	0.4		300	75.0	1.5	
Brazil	176	70.3	0.8		218	76.5	2.1	
Total for the 10 countries	3339		1.33		4067		2.56	

Source: US Census Bureau, International Data Base, August 2004.

Pattern of drug usage in the elderly

Before discussing the impact of any age-related changes in drug response and the current regulatory framework supporting the development of drugs in the elderly, it is worth asking whether the medications already available are used appropriately in this population. The broad aims of treatment in this group are improving morbidity and prolonging survival without any adverse effect on quality of life. A number of studies have reported on the use of inappropriate medications in the elderly while others have focused on underutilization of appropriate medications. Such prescribing patterns have important consequences in terms of frequencies of adverse drug reactions (ADRs), hospitalizations and mortality in the elderly as well as implications for healthcare and economic resources.

A PubMed search by the author in February 2004, using the combination of key words 'inappropriate use of drugs' and 'elderly', retrieved 372 citations (although each citation was not individually scrutinized). In one study of 603 hospitalized patients with a mean age of 79 years, a total of 376 patients (62%) were discharged on digoxin. There was no indication for its use in 223 (37%) patients. Half of the patients in whom digoxin was not indicated were actually given the drug. Furthermore, 38 (29%) of the 132 patients without an indication and not already on digoxin were initiated on it [1]. Onder *et al.* have reported that during their hospital stay, 837 (14.6%) of 5734 patients (mean age 79 years) admitted to geriatric or internal medicine wards received one or more medications classified as inappropriate on the basis of Beers criteria [2]. Ticlopidine ($n = 346$) was the most frequently used medication, followed by digoxin ($n = 174$) and amitriptyline ($n = 113$). The particular drugs used inappropriately vary from time to time and from hospital to hospital. However, all studies reveal that a large number of drugs are prescribed inappropriately to the elderly.

The most important determinant of the risk of receiving an inappropriate medication is the number of drugs being taken. One multicentre study during the period 1988 and 1997 reported 1704 ADRs in 28 411 patients consecutively admitted to participating centres [3]. In 964 cases (3.4% of all admissions), ADRs were the cause of these hospital admissions. Of these, 187 ADRs were classified as severe. The mean age of the patients was 70 ± 16 years. In 397 frail elderly inpatients (46.4% were aged ≥75 years), Hanlon *et al.* reported that 365 patients had at least one medication rated as inappropriate [4]. Some of the most common problems involved expensive drugs (70.0%) and impractical (55.2%) or incorrect directions for use (37.5%). Other problems related to dose and interactions. In this study, 169 patients were taking drugs for

which there was no indication. A wide range of drug classes was implicated in inappropriate use. These included cardiovascular (10.77%), gastrointestinal (9.12%), central nervous system (4.22%), respiratory (4.11%), hormones (4.01%), blood products (3.36%) and antimicrobials (2.56%) among others. In terms of number of patients involved, the most common drug classes used inappropriately were gastric (50.6% of patients), cardiovascular (47.6%) and central nervous system (23.9%) drugs.

In contrast to inappropriate use, there is also a serious problem of underutilization of appropriate medications. 'Statin' therapy is known to be associated with reduced mortality in all age groups, including very elderly individuals, with significant coronary artery disease. Elderly patients were significantly less likely to receive 'statins' than younger patients (< 65 years 28.0%, 65–79 years 21.1%, and ≥80 years 19.8%) [5]. Similar underuse of 'statin' was reported in another study of 622 eligible patients with previously established coronary artery disease and hyperlipidaemia. Only 230 (37%) of these patients had received these hypolipidaemic drugs [6]. One of the studies has provided further worrisome evidence showing that the elderly >65 years old as well as females were less likely to be prescribed aspirin, β-blocker and a statin in the secondary prevention of ischaemic heart disease in primary care [7]. The concern from these observations arises from the fact that older patients receive a greater absolute risk reduction than younger individuals, and yet they were less likely to receive a 'statin' therapy. A study on the use of lipid-lowering drugs in the UK revealed similar trends. Although the use of 'statins' had increased over time, 33% of these patients were still receiving only an equivalent of <20 mg simvastatin daily. In 1998, the odds ratios for receiving a 'statin' therapy were 1 in the age band 55–64 years, 0.64 in the age band 65–74 years and 0.16 in the age band 75–84 years. This age effect was similar in those with and those without a major comorbidity [8].

Similarly, underuse of effective medicines in the elderly has been reported with antihypertensive drugs [9] and antiplatelet or anticoagulant therapy [7, 10, 11]. β-Blockers following acute myocardial infarction (AMI) [7, 12] are also underused but this seems to have improved recently [13]. Underinvestigation and undertreatment of chronic heart failure have been shown to persist. Failure to treat elderly patients with angiotensin converting enzyme (ACE) inhibitors is associated with a mortality that appears to be greater than that seen in the placebo arms of large clinical trials of ACE inhibitor therapy [14, 15].

Jackson *et al.* have provided a number of reasons for suboptimal prescribing [16] while others have commented on improving quality of prescribing and access of the elderly to the medications [17]. While underprescribing is a problem that can be remedied through physician education, noncompliance by patients themselves continues to present a challenge in the care of not only the elderly but also their younger counterparts. Persistence with 'statin' therapy in older patients declines substantially over time, with the greatest drop occurring in the first 6 months of starting treatment [18, 19]. With regard to the use of β-blockers, patients not discharged on β-blockers are unlikely to be started on them as outpatients. For patients who are discharged on β-blockers after AMI, there is a significant decline in use after discharge [20].

Age-related changes in pharmacology

Pharmacokinetics and pharmacodynamics of a drug are the two determinants of its dose–response relationship, both of which exhibit large interindividual variability. This variability arises from their modulation by factors such as age, gender, comedications or comorbidity (e.g. renal or hepatic dysfunction). There may be age-related up- or downregulation of pharmacological targets responsible for the pharmacodynamic effects of a drug. This variability also arises from genetic influences that regulate the expression of drug-metabolizing enzymes or the responsiveness of various pharmacological targets. The presence of variant alleles often exerts influences that usually far exceed those due to the other covariates stated above.

Contrary to what is often claimed, there is little evidence to demonstrate that age *per se* has a major effect on the pharmacology of a drug. Table 2 summarizes the prevalence of various covariates that influence the pharmacokinetics of a drug in the elderly relative to young

Table 2
Relative prevalence of various covariates that influence the pharmacokinetics

Covariate	Young adults	Elderly
Liver disease/CYP3A4	+	++
Genetics/CYP2D6	+	+
Genetics/CYP2C9/19	+	+
Renal disease	+	+++
Cardiac disease	–	++
Polypharmacy	+	++++

adults. Therefore, any age-related differences in the prevalence of these covariates may be expected to give rise to age-related changes in the pharmacology of the drug when the group is evaluated as a whole. Unless these changes are taken into account when prescribing, they may impact adversely on dose–response relationship and therefore, on the clinical efficacy, safety and risk–benefit of a drug.

Age-related changes in pharmacokinetics

One of the earliest, and perhaps the most striking, example of a drug that provided alarming evidence of age-related changes in its pharmacokinetics was benoxaprofen.

Benoxaprofen was a novel nonsteroidal anti-inflammatory drug (NSAID) introduced in 1980. The drug was launched amidst massive publicity and its marketing was 'explosive'. The resulting uptake of the drug in clinical practice was overwhelming. Not surprisingly, reports of serious ADRs (photosensitivity and hepatotoxicity in this case) began to appear at an alarming rate. Benoxaprofen-induced hepatic injury was typically a progressive painless jaundice (cholestasis with little or no necrosis) and usually associated with nephrotoxicity. Its incidence was estimated to be about 2–4% and the mortality rate high. By August 1982, there were 61 fatalities reported and the marketing authorization of the drug was suspended immediately. Age was identified as a risk factor. Subsequent studies in otherwise healthy individuals showed that the half-life of benoxaprofen was of the order of 110 h in the elderly [21, 22] in contrast to 16–35 h in young adults [22, 23]. Renal insufficiency did not induce major changes in pharmacokinetic parameters in one study [24] while another reported a correlation between creatinine clearance and elimination half-life and plasma clearance of benoxaprofen [25]. Of the administered dose of benoxaprofen, only 13.9% is recovered in the urine over a 24-h period. However, since renal clearance accounts for 33% of total clearance, benoxaprofen kinetics may be influenced by severe renal impairment [24].

Terodiline is a more recent example of a drug with similar age-related differences in its half-life. The mean half-life of terodiline was 131 h (range 63–237) in the elderly in contrast to only 57 h (range 35–72) in young adults [26]. It was originally marketed in Sweden in 1965 as an antianginal drug. However, severe urinary retention proved to be a frequent side-effect and it was therefore re-developed in the late 1980s for the treatment of urinary incontinence. Approved in July 1986, it was withdrawn from the market in September 1991 following 69 reports of serious cardiac arrhythmias associated with its use. This included torsade de pointes (TdP), a unique form of polymorphic ventricular tachycardia associated with prolongation of the QTc interval. An analysis of predisposing factors in the 69 reports identified an age of >75 years as one of the potential risk factors.

There are very few drugs for which such striking differences in half-lives between the elderly and the non-elderly have been demonstrated in absence of any obvious cause. However, the presence of various modulating factors could explain the observed age-related differences in the pharmacokinetics of other drugs [27, 28]. Age-related changes in pharmacokinetics due to impaired drug clearance are a frequent cause of, and major contributor to, drug toxicity in the elderly.

Drug distribution may be altered in the elderly. The relative lipid content increases markedly with age. Body fat increases from 19% at the age of 25 to 35% at the age of 70 years in males and from 33% to 49%, respectively, in females [29]. Total body water content and lean body mass also fall with advancing age. The effect of these changes is to decrease the volume of distribution of polar (water-soluble) drugs such as cimetidine and morphine and to increase that of nonpolar (lipid-soluble) drugs such as benzodiazepines. Increase in volume of distribution often results in retention and prolonged half-lives of the drugs concerned. For most drugs, however, these age-related changes in body composition do not have a significant effect on volume of distribution [30].

Serum albumin decreases from 4% in younger adults to 3.5% in those over 80 years old [31]. The concentration of α_1-acid glycoprotein that is responsible for binding many basic drugs tends to increase with age [32]. Changes in plasma proteins can be clinically significant for drugs with a narrow therapeutic index. However, the effect of age on protein binding is generally unpredictable. Total serum haloperidol levels have been reported to show a linear relationship with daily dose with no difference in the total haloperidol level per daily dose between the elderly and younger adults [33]. However, in this study of 59 patients aged 50–88 years, the free fraction increased with age. No doubt, there are a few other similar examples. In contrast, plasma protein binding of celecoxib or diclofenac was unaffected by age [34]. Alterations in plasma protein binding that occur in the elderly are generally not attributed to age, but rather to physiological and pathophysiological changes or disease states that may occur more frequently in the elderly. In general, only a few drugs show a change of more than 50% in their free fraction in the elderly.

The activity of some drug-metabolizing enzymes

responsible for phase I oxidation may be impaired in old age. Phase II conjugation reactions appear to be much less susceptible. Overall, it is estimated that drug-metabolizing capacity is reduced by approximately 30% after the age of 70 years [35]. Other studies have suggested that specific activities of phase I drug-metabolizing enzymes are not reduced with age *per se* and that there is no change in the enzyme affinity for their substrates [36]. Rather, an important contribution to reduced hepatic elimination of drugs comes from reduction in liver size and blood flow with advancing age [36, 37]. Metabolism could also be impaired due to the presence of liver disease. Normal liver function is an important determinant of the activity of CYP3A4 that metabolizes a large number of drugs widely used clinically. It is an enzyme that is highly susceptible to liver disease. This is in contrast to CYP2D6, which is relatively refractory to liver disease. The susceptibility of other major CYP drug-metabolizing enzymes appears to be intermediate between that of CYP3A4 and CYP2D6 [38–41]. Intercurrent stresses such as community-acquired pneumonia, a fracture or hip replacement surgery have been shown to reduce the activity of aspirin esterase in older patients [42, 43].

For many of the alleged age-related changes in protein binding, fat content and drug metabolism, the evidence is modest and not consistent. By comparison, age-related deterioration in renal function is more critical and well characterized. It results in accumulation of many drugs and/or their metabolites that are cleared predominantly by the renal route. Glomerular filtration rate declines with age, with a mean of 35% reduction in older people compared with their younger counterparts [44]. Renal tubular function also declines with resulting impairment of excretion of drugs by active tubular secretion. Unexpectedly, however, renal disease also influences the activity of drug-metabolizing enzymes. Animal studies in chronic renal failure have shown a major downregulation (40–85%) of hepatic cytochrome P450-mediated metabolism by specific CYP enzymes. Phase II reactions such as acetylation and glucuronidation are also involved, with the activity of some enzymes induced and others inhibited [45]. Animal studies have also suggested the presence of circulating uraemic factor(s) in the serum that downregulates the activity of CYP enzymes by 30–35% secondary to reduced gene expression [46, 47]. End-stage renal disease is associated with inhibition of hepatic enzymes exhibiting genetic polymorphisms such as N-acetyltransferase-2 (NAT-2), which is responsible for the rapid and slow acetylator phenotypes. This inhibition is reversed by transplantation [45, 48]. There is substantial evidence suggesting that it may be possible to remove by dialysis the inhibitory factors circulating in the serum in end-stage renal disease patients [45]. Patients with end-stage renal disease are at an increased risk of drug toxicity due to reduced activity of the CYP3A enzyme pathway [49]. Similarly, CYP2D6 activity in man is also compromised in parallel with deterioration of renal function [50]. In patients with end-stage renal disease, the plasma S/R warfarin ratio is 50% higher than in control group (0.82 *vs.* 0.55; $P < 0.03$). There was no correlation between warfarin dose and plasma S/R warfarin ratio. This probably reflects a decrease in CYP2C9 activity [51]. The effect of moderate renal insufficiency on hepatic drug metabolism is not as well characterized and requires investigation.

Age-related pharmacokinetic changes in perspective

When age-related changes in pharmacokinetics are put in perspective, it is evident that gender, ethnicity or the genotype of a patient frequently has a far greater effect. CYP3A4 is responsible for the metabolism of nearly 50% of drugs metabolized by oxidation. The activity of this enzyme appears to be unaffected by age over the range of 27–83 years, suggesting that any age-related changes in the clearance of CYP3A4 substrates are secondary to changes in liver blood flow, size, or drug-binding and distribution with ageing [52]. Even the presence of food in the stomach can markedly alter the pharmacokinetics of some drugs.

Age-related changes in pharmacokinetics are typically investigated in a panel of subjects aged ≥65 years and who are otherwise healthy – a population that is not easy to find. Subjects who have renal or hepatic impairment are excluded from randomization and the influence of these two variables is investigated in separate studies. The pharmacokinetic parameters in this elderly panel are compared with those from a younger panel (about 30–40 years of age). It is neither possible nor intended to generalize, but in broad terms, the mean data from a number of drugs show that changes in pharmacokinetics due to age *per se* are very modest (of the order of 20–40%) when compared with the influences of other covariates such as food, gender, comorbidity, comedications and genetic factors (of the order of 50–300%). There are of course exceptions to this.

Age-related changes in pharmacodynamics

Only recently has interindividual variability in pharmacodynamic response to drugs attracted academic, regulatory and clinical interest. It is generally acknowl-

edged that at a given drug concentration, the elderly are more susceptible to certain pharmacological effects [53, 54]. These include anticholinergic, dopaminergic and proarrhythmic effects. It is probable that there is age-related up- or downregulation in the pharmacological responsiveness of the corresponding pharmacological targets.

With advancing age, there are changes in central neurochemical transmission. For example, pre- and postsynaptic neurochemical markers of the central cholinergic system decline [55] while dopamine D2 receptor subtypes decrease [56] and dopamine D1 receptor subtypes increase [57]. The concentrations of noradrenaline in the hypothalamus decline [58] whereas responses to serotonergic drugs vary with advancing age. Although the total brain serotonin declines with age, the change is much less evident in the hindbrain [59, 60]. There is a significant reduction with age not only in the 5-HT_{1D} and 5-HT_2 serotonin receptor sites but also in 5-HT_2 serotonin binding affinity in the frontal cortex [61]. Autonomic reflexes are significantly altered in the older population. β-Adrenoreceptor sensitivity declines with age [62], particularly with regard to inotropic and chronotropic responses.

The anticholinergic effects of some antidepressants and neuroleptic drugs are often responsible for agitation, confusion, and delirium in the elderly. The use of heterocyclic antidepressants in the elderly is frequently limited by anticholinergic and/or cardiovascular side-effects. This has resulted in a significant change in the pattern of antidepressant use in the elderly from tricyclic antidepressants to selective serotonin reuptake inhibitors (SSRIs) that are devoid of anticholinergic effects. Apart from antidepressants, the use of antiarrhythmic therapy in the elderly is also complicated by their anticholinergic properties. Similarly, tardive dyskinesia has been strongly associated in the elderly with the use of older typical neuroleptics with high affinity (blockade) for the dopamine D2 receptor. Not surprisingly, the elderly are more sensitive to the autonomic and extrapyramidal effects of neuroleptics. Newer atypical antipsychotics, while showing similar efficacy to conventional antipsychotics, induce lower rates of motor disturbances [63] and are now the preferred class in the elderly. TdP is a potentially fatal ventricular tachycardia induced by a number of non-antiarrhythmic drugs that prolong the QTc interval. Cardiac disease, especially cardiac failure, is a major risk factor since potassium channels are often downregulated in diseased myocardium. Apart from the higher prevalence of cardiac failure in the elderly, it has been shown that a significant correlation exists between ageing and prolongation of the QTc interval [64]. Not surprisingly, age is one of the risk factors for drug-induced TdP.

Pharmacogenetics and the elderly

Although not widely appreciated, genetic factors may play as important a role in the elderly as they may in the younger population. A number of drug-metabolizing enzymes are expressed polymorphically in the population [65]. The impact of these polymorphisms in the safe and effective use of drugs in the elderly is most evident during induction of anticoagulation with warfarin that is metabolized predominantly by CYP2C9 [66]. Available data support the view that although the CYP2C9*3/CYP2C9*3 genotype is associated with dramatic over-anticoagulation soon after the introduction of oral anticoagulants, overdose during the maintenance period is mostly related to environmental factors [67]. It is also recognized that interindividual variability in warfarin sensitivity also originates from environmental factors. In one study, age and CYP2C9 genotype accounted for 12% and 10% of the variation in warfarin dose requirements, respectively [68].

CYP2D6 polymorphism is responsible for the metabolism of a large number of cardiovascular and psychoactive drugs and is therefore of particular relevance to the use of drugs in the elderly. Studies beginning in 1977 have shown that any given population may be divided into two phenotypes – extensive metabolizers (EMs) or poor metabolizers (PMs) – depending on their ability to mediate CYP2D6-dependent hydroxylation of the (now obsolete) antihypertensive drug debrisoquine [69]. Advances in molecular genetics over the last decade have allowed CYP2D6 metabolic capacity to be assigned by direct genotyping of the patients. This polymorphism results from autosomal recessive inheritance, in a simple Mendelian fashion, of variant alleles at a single locus. Those individuals who carry two CYP2D6 inactivating alleles are phenotypic PMs. Within the EMs, there are two subgroups of particular interest at either extreme of the EM population distribution. One subgroup, termed the ultrarapid metabolizers (UMs), is comprised of individuals possessing multiple copies of the alleles (CYP2D6*1 and CYP2D6*2) responsible for normal metabolic capacity [70]. The presence of two specific CYP2D6 alleles, CYP2D6*35 and CYP2D6*41, is also thought to confer ultrarapid metabolizing capacity even in the absence of gene duplication [71]. The other subgroup, termed the intermediate metabolizers (IMs), is comprised of a heterozygous genotype ('gene-dose effect'). UMs metabolize

drugs so avidly that despite being prescribed high doses, they attain very low concentrations of the parent drug and high levels of rapidly accumulating metabolites while IMs display a modest impairment in drug-metabolizing capacity. The pharmacokinetic consequences arising from CYP2D6 polymorphism are shown in Table 3.

Age *per se* does not seem to affect or modify genetically determined differences (between EMs and PMs) in the pharmacokinetics of drugs metabolized by CYP2D6 and CYP2C19 [72]. The expression of P-glycoprotein activity, important in the disposition of many drugs, is also under the control of *MDR1* (multidrug resistance) gene and shows considerable interindividual variability. Interactions at these transporters and/or P-glycoprotein have explained many drug interactions previously considered to be bizarre (e.g. convulsions following coadministration of certain fluoroquinolones with nonsteroidal anti-inflammatory drugs or loperamide-induced respiratory depression when it is coadministered with quinidine). In respect of susceptibility to drug interactions at these sites, there are no reasons to believe that there are any age-related differences.

Genetic factors also influence the responsiveness of various pharmacological targets. Their contribution in the elderly may be so easily overlooked because of the presence of other comorbidity. Polymorphisms of β_2-adrenoceptors or of the core promoter of 5-lipoxygenase (ALOX5) have already been shown to influence the bronchodilatory response to salbutamol [73, 74] or ALOX5 inhibitors such as zileuton [75], respectively. Some β_1-adrenoceptor or β_2-adrenoceptor polymorphisms have been related to survival in patients with cardiac failure [76–78]. Recently, it has been demonstrated that the presence of specific genetic mutations in the promoter region of serotonin transporter (5-HTT) gene is predictive of response to SSRIs. Patients who had one or two copies of the long variant (homozygous l/l or heterozygous l/s) had a better therapeutic response than patients who were homozygous for the short variant (s/s) [79–81].

From a pharmacogenetic study of antidepressant intolerance in elderly patients, Murphy *et al.* [82] reported that discontinuations due to paroxetine-induced side-effects were strongly associated with 5-HT_{2A} genotype and that pharmacodynamic differences (5-HT_{2A} variants) appeared to be more important than pharmacokinetic differences (CYP2D6 variants). However, such pharmacogenetic observations are not unique to any particular age group.

Table 3
Pharmacokinetic consequences of CYP2D6 polymorphism

Pharmacokinetic parameter	Consequences for the PM relative to EM
Bioavailability	2–5-fold
Systemic exposure	
C_{max}	2–6-fold
AUC	2–5-fold
Half-life	2–6-fold
Metabolic clearance	0.1–0.5-fold

Age-related differences in drug safety

Adverse drug reactions in the elderly

It is often claimed that adverse drug reactions (ADRs) are more frequent in the elderly. This may be true for a few drugs, but for most drugs these claims are often based on inadequate data on drug usage and, hence, rates per population exposed. Nor do these claims take into account the role of other contributory factors such as renal dysfunction or polypharmacy. It is questionable if age *per se* is a cause of increased risk of ADRs [83, 84].

Spontaneous ADR-reporting systems have many limitations but there is no evidence that reporting is biased by age or gender. Although about 55% of the drug prescriptions dispensed in the community in 2001 were for the elderly population, the reporting rates for ADRs generally in the elderly did not correspond to this level of exposure. For example, in the year 2000, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) received 33 139 spontaneous reports of ADRs. Of these, 10.6% related to patients aged ≥71 years and 82.2% related to patients aged ≤70 years. Age was not specified on 7.2% of the reports. The corresponding numbers for the years 2001 and 2002 were 21 465 (15.3%, 77.2% and 7.5%) and 16 279 (19.2%, 71.7% and 9.1%) reports, respectively. Indeed, female gender seemed to be a greater risk factor, with nearly 60% of these reports citing female patients (personal communication). For example, females are almost twice as likely to experience drug-induced torsade de pointes (TdP) [85], hepatotoxicity [86] or nephrotoxicity [87].

The elderly, however, appear to have a higher relative risk of toxicity associated with a few specific drugs or specific pharmacological actions. For example, the reporting rates of terodiline-induced proarrhythmias were estimated at one case in 22 321 patients below 50 years of age, one in 6464 patients aged 51–60 years, one in 4772 patients aged 61–70 years and one case in

2978 patients for those above 71 years. Non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin in doses <500 mg daily, are associated with gastrointestinal haemorrhage. This class of drugs is widely used in the elderly as well as by the younger population. There are surprisingly few data on the extent to which age *per se* might be a risk factor. Available evidence certainly suggests that the elderly are indeed at a higher relative and attributable risk [88–93]. The higher risk in the elderly may be related to the presence of a number of risk factors such as the use of higher dose, comorbidity and comedications (such as steroids, other antiplatelet agents or anticoagulants) [92] or mucosal damage resulting from *Helicobacter pylori* infection [94]. The elderly do appear to have a clinically different presentation [95]. Nephrotoxicity due to cycloxygenase-2 selective NSAIDs, for example, is also reportedly more frequent in the elderly. The median ages of 122 cases of nephrotoxicity with celecoxib and 142 cases with rofecoxib were 72 and 75 years, respectively [87]. However, the presence of major risk factors such as pre-existing renal impairment, heart failure, liver dysfunction and the use of angiotensin converting enzyme (ACE) inhibitors or diuretics may have contributed greatly in this population.

Drug–drug interactions in the elderly

One review of the available studies suggests that up to 30% of hospital patients and 70% of ambulatory patients could be receiving potentially interacting drugs [96], accounting for many hospital admissions [97]. In view of multiple comorbidities, the elderly are at a special risk of drug–drug interactions since they also consume a greater number of drugs. In the year 2001, the number of prescriptions dispensed per head by community pharmacists in the UK was 4.2 for patients aged <16 years, 6.6 for those between 16 and 59 years and 28.7 for patients aged ≥60 years (Department of Health Prescription Statistics, 15 November 2002). The point to be emphasized is that most important metabolic drug–drug interactions are independent of the patient's age *per se*. An analysis of predisposing factors in the 69 reports of terodiline-induced proarrhythmias identified potential interactions with concurrent use of cardioactive medications, diuretics, antidepressants or antipsychotic agents. A recent study by Juurlink *et al.* makes a number of valuable points [98]. Apart from excluding age *per se* as a risk factor, their data showed a high prevalence of renal disease (23–59%) and polypharmacy in the elderly. The three drug interactions examined by these investigators could all be easily explained by mechanisms already known. One of these interactions, between ACE inhibitors and potassium sparing diuretics, is so well known that it is a matter of great concern that the combination should have been prescribed to so many octogenarian patients with a high prevalence of renal dysfunction!

Since the majority of drugs are metabolized by CYP2D6, CYP3A4 and CYP2C19, polypharmacy increases the potential for drug interactions either by inhibition of drug metabolism or by interference with nonmetabolic drug clearance processes. Metabolism of a drug may be inhibited by coadministration of an inhibitor of drug metabolism or of two substrate drugs competing for the drug-metabolizing enzyme. The resulting pharmacokinetic changes can be profound and of considerable clinical significance if the drug has a narrow therapeutic index. Studies with dofetilide, quinidine, digoxin and a host of other drugs have identified renal tubular cation transporters as an important site of clinically significant drug–drug interactions [99].

Less well appreciated during the clinical use of drugs are the drug–drug interactions at the pharmacodynamic level such as alterations in the responsiveness of pharmacological targets due to concurrent administration of two drugs with either agonist or antagonist activities. Such pharmacodynamic drug–drug interactions are also proving to be a major source of concern. Frequent concurrent use of two neuroleptics [100] or two QT-prolonging drugs [101, 102] has been reported. In one study it was found that at least two neuroleptics were prescribed simultaneously on 73% of treatment days in Badajoz (Spain), 46% in Huddinge (Sweden) and 46% in Tartu (Estonia). The authors' conclusion that polypharmacy in schizophrenic patients is an international practice is a matter of clinical concern [103]. The main finding of another survey was that 27.5% of schizophrenic patients were discharged on an antipsychotic polypharmacy regimen and yet there was no evidence-based support for such polypharmacy [104]. When two neuroleptics are prescribed concurrently, there is a risk of interactions not only at the pharmacodynamic level but also at a pharmacokinetic level if they are both metabolized by the same CYP enzyme, e.g. CYP2D6. Similarly, most QT-prolonging drugs are metabolized by CP3A4 and when two QT-prolonging drugs are prescribed concurrently, there is a risk of interactions not only at the pharmacodynamic level but also at a pharmacokinetic level.

Frail elderly

The frail elderly are a unique subgroup of patients within a subgroup. They probably represent a pheno-

type at the extreme end of variability in the dose–concentration–response relationship of a drug. Although the term 'frailty' is widely used, there is no consensus on its meaning and no clear guideline(s) for identifying and describing older adults as frail. The traditional notion of frailty is an inevitable decline in abilities usually associated with physical aspects of ageing. More recent concepts of frailty reflect an interaction between a number of individual factors and environmental elements. Interleukin (IL)-6 is a proinflammatory cytokine that is normally expressed at low levels, except during infection, trauma, or other stress. IL-6 has been proposed as a mediator of certain of the phenotypic changes of advanced age, particularly those that resemble chronic inflammatory disease, including frailty [105]. In cohorts of frail, older individuals, tumour necrosis factor (TNF)-α and IL-6 also act as disease markers. Circulating levels of TNF-α seem to predict best the mortality in frail, elderly populations, whereas IL-6 seems to be a strong marker of risk in healthy, elderly populations [106].

It is worth emphasizing that frailty can occur at any age, but clearly, it is highly prevalent in old age. It confers high risk of disability, hospitalization, and mortality and has often been considered synonymous with disability, comorbidity, and other characteristics. However, frailty is not synonymous with either comorbidity or disability. Rather, comorbidity is thought to be an aetiological risk factor for frailty and disability is an outcome thereof. It is now recognized that it may have a biological basis and be a distinct clinical syndrome [107, 108]. Lower serum cholesterol levels have been considered an independent biochemical marker of frailty in elderly hospitalized patients [109]. Low serum albumin and iron are also considered markers of frailty and poor health [110, 111]. Sarcopenia, a term used to define loss of muscle mass and strength that occurs with ageing, is believed to play a major role in the pathogenesis of frailty and functional impairment that occurs with old age. Frailty aggravates age-related changes in protein metabolism by inducing increased catabolism of muscle protein and a decrease in muscle mass [112].

Not surprisingly, elderly frail individuals may display profound changes in pharmacokinetics and pharmacodynamics of a drug. Paracetamol clearance expressed per unit volume of liver showed no difference between fit young and fit elderly subjects, but it was significantly reduced in the frail subjects [113]. Plasma aspirin esterase activity was found to be similar in a group of healthy elderly adults, a group of young adults and a group of frail young adults, but was lower in a sample of frail elderly subjects [114]. In frail elderly people, this was later shown to be due to a reduction in the quantity of enzyme present [115]. In a pharmacokinetic study of oxybutynin, there was a trend towards increasing peak plasma levels and bioavailability with increasing age and frailty. The differences were more apparent between the active elderly and frail elderly groups than between the active elderly and young volunteers [116]. A pharmacokinetics and pharmacodynamics study following oral and intravenous administrations of metoclopramide reported that the more frequent sedation observed in frail elderly might reflect associated pharmacodynamic changes in specific receptor or target sites [117]. O'Mahony has reviewed the data showing reduction in phase 2 drug metabolism in the frail elderly in comparison with the fit elderly and young elderly [30]. Nutrition and nutritional status may influence the metabolism of drugs and, conversely, drugs may impede the nutritional status of individuals. The challenges posed by the unique phenotype of the frail elderly are further magnified by inappropriate use and inappropriate medications and other problems associated with this poor prescribing [4].

Growth hormone has been considered for the therapeutic treatment of frailty associated with ageing and various acute and chronic catabolic conditions. Growth hormone secretagogues such as capromorelin are being evaluated for the treatment of musculoskeletal frailty in elderly adults [118]. An improvement in the protein status of frail elderly persons will in all likelihood have consequences for drug response [119].

Regulatory framework for the development of drugs in the elderly

The discussion in Part I of this paper on prescribing patterns, age-related changes in pharmacology and the covariates responsible for these changes provides a helpful background against which to consider the adequacy (or otherwise) of the regulatory framework that supports drug development in the elderly.

Regulatory authorities have long recognized the roles of age, gender, ethnicity, genetics, comorbidity and comedications in influencing the safe and effective use of medicines. Not surprisingly, they have issued a number of guidelines to ensure that these factors (and any others specific to individual drugs) that are relevant to the choice of correct dose in the elderly are fully explored during drug development. These guidelines are listed in Table 4. In light of the influences of these factors, the recommended dose and dosing regimen require

Table 4
Committee for Proprietary Medicinal Products (CPMP) and International Conference on Harmonization (ICH) regulatory guidelines relevant to the development of drugs in the elderly

1. CPMP Guidance on Pharmacokinetic Studies in Man*
2. ICH Note for Guidance on Dose Response Information to Support Drug Registration
3. CPMP Note for Guidance on the Investigation of Drug Interactions
4. ICH Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data
5. ICH Note for Guidance on Studies in Support of Special Populations:
   5a Geriatrics
   5b Pharmacokinetics in renally or hepatically impaired patients
6. CPMP Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function
7. CPMP Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function

**This guideline can be accessed on: http://pharmacos.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc3aen.pdf All other guidelines can be accessed on: http://www.emea.eu.int/sitemap.htm*

justification in the dossier. It is evident that the current guidelines already recommend investigation of the influences of important covariates that are over-represented in the elderly.

From the foregoing discussions, the dosing implications of the changes in pharmacokinetics, due to genetic as well as nongenetic influences, are self-evident. Both nortriptyline (an antidepressant) and perhexiline (an antianginal) are metabolized by CYP2D6. For therapeutic effect, most UMs require nortriptyline doses of 300–500 mg daily (even higher in rare individuals) in contrast to PMs who need only 20–30 mg daily [120]. Perhexiline, marketed at doses of 100 mg three times a day, was withdrawn from the market in 1988 because of neuropathy and hepatotoxicity associated with its use. PMs of CYP2D6 are at a much greater risk of developing these side-effects. A recent study has shown that safe doses of perhexiline in UMs, EMs and PMs of CYP2D6 are 300–500 mg, 100–250 mg and 10–25 mg daily, respectively [121]. Kirchheiner *et al.* have recently reviewed CYP2D6 and CYP2C19 genotype-based dosing recommendations for antidepressants. Needless to say that these apply to the elderly as well [122]. Various guidelines from the European Union's Committee for Proprietary Medicinal Products (CPMP) recommend the sponsors of new chemical entities (NCE) to explore the impact of genetic factors on the dose–concentration–response relationship of a drug.

Such is the concern regarding drug interactions that the CPMP has adopted a guideline on 'Drug Interactions'. This guideline makes recommendations on interaction studies on NCEs on the basis of their physicochemical, pharmacokinetic and pharmacodynamic properties as well as on the likelihood of two drugs being coadministered. It defines an interaction as clinically relevant (i) when the therapeutic activity and/or toxicity of a drug is changed, or (ii) when concomitant use of the two interacting drugs is likely to occur when used as therapeutically recommended. The US Food and Drug Administration (FDA) and the Japanese Ministry of Health, Labour and Welfare (MHLW) have also issued similar guidelines.

Two guidance notes, however, are of special interest. The International Conference on Harmonization (ICH) Note for Guidance on 'Studies in Support of Special Populations' requires that 'the overall database of the dossier should be examined for the presence of age-related differences, e.g. in adverse events rates, in effectiveness, and in dose–response. If these relatively crude overview analyses show important differences, further evaluation may be needed'. The ICH guideline on 'Dose–Response Information to Support Drug Registration' requires that 'In utilizing dose–response information, it is important to identify, to the extent possible, factors that lead to differences in pharmacokinetics of drugs among individuals, including demographic factors (e.g. age, gender, race), other diseases (e.g. renal or hepatic failure), diet, concurrent therapies or individual characteristics (e.g. weight, body habitus, other drugs, metabolic differences)'. Both these guidelines, like all other ICH guidelines, are promulgated and enforced by the FDA in the USA, CPMP in the EU and the MHLW in Japan as well as by other non-ICH regulatory authorities.

In addition to these general guidelines, there is a

set of 'therapeutic' guidelines that make recommendations on clinical trials in specific therapeutic areas of special relevance to the elderly. These include guidelines on osteoarthritis, anticancer drugs, schizophrenia, depression, Parkinson's disease, Alzheimer's disease, cardiac failure and urinary incontinence, to list a few.

A third set of 'biostatistical' guidelines provides guidance on the statistical robustness of clinical trials in terms of study designs, statistical power, choice of comparators and analyses of the results. One of these – 'Statistical Principles for Clinical Trials', CPMP/ICH/363/96 – recommends that an adjustment for the influence of covariates or subgroup effect is an integral part of the planned analysis. Age is one of the covariates included in this.

All these guidelines except one can be accessed on website of the European Medicines Agency (EMEA) at the following address under 'Regulatory Guidance and Procedures' at http://www.emea.eu.int/sitemap.htm The exception is the CPMP 'Guidance on Pharmacokinetic Studies in Man' that can be accessed at http://pharmacos.eudra.org/F2/eudralex/vol-3/pdfs-en/3cc3aen.pdf

Determining the right dosing regimen

The dose of a drug is relevant only to the extent that it determines the plasma concentration. For reasons discussed earlier, the elderly at a given dose may experience exposure that is different from younger adults. Furthermore, there is considerable interindividual variability within not only the elderly but also their younger counterparts, often with a significant overlap. In addition, the optimal therapeutic plasma concentrations have often not been established for most drugs in any age group, including the elderly.

Determining the right dose in the non-elderly

The problem of identifying a correct dosing regimen is not specific or limited to the elderly. It appears to be a general one affecting not only a range of population subgroups such as females, ethnic minorities and children, but also a wide range of therapeutic classes. It is interesting to note that racial/ethnic groups are also under-represented in clinical trials. In one study of NCEs approved between 1995 and 1999, there were only 18 of the 98 drugs (where race/ethnicity was assessed) that showed a difference based on race/ethnicity [123]. The effects are primarily pharmacokinetic differences ($n = 9$; 50%), efficacy difference ($n = 7$; 39%) and safety ($n = 2$; 11%).

Despite often conducting adequate dose-finding studies, the sponsors in their attempt to maximize efficacy take forward the highest effective dose (from their dose-ranging studies) for investigation in pivotal studies. It is therefore not surprising that postapproval dose reductions are frequent once a drug is in routine clinical use. In one study that examined all 499 labels of drugs approved by the FDA between 1 January 1980 and 31 December 1999 for significant dose changes, 73 (21%) of the 354 evaluable labels had registered a dose change. Of these, 58 (79%) were safety-motivated dose reductions. When adjusted for relative risk, this was the highest (2.26) for drugs approved originally during the period 1995–1999 (with baseline risk for drugs approved during 1980–1984 being set at 1.00) [124]. In another study, it was reported that of the 48 drugs examined, about 40 were found to be just as effective at doses of 60% or lower than those recommended [125]. The dosages of β-blockers shown to be effective in randomized trials are not the doses commonly used in clinical practice, and treatment with lower dosages of β-blockers are associated with at least as great a reduction in mortality as treatment with higher dosages. It appears that doses lower than those recommended initially often have a better risk–benefit ratio. Because of the presence of covariables that influence the pharmacology of a drug, the elderly may require even lower doses of some drugs than their younger counterparts. However, even when β-blockers are prescribed to the non-elderly, the dosages used are still considerably lower than those proved to be effective in preventing death after myocardial infarction.

Determining the right dose in the elderly

Among the population groups that are consistently under-represented in preapproval clinical trials are the elderly, generally defined as those above 65 years of age [28, 126]. One review analysed a total of 9664 subjects who were enrolled in trials studying osteoarthritis and rheumatoid arthritis. Although more than half of the studies reviewed included patients ≥65 years of age, there were only 207 (2.1%) patients in this older age group. While there was inclusion of the 'young-old' (65–74 years of age), only 14 of the 9664 patients studied were between 75 and 84 years of age, with none representing those aged ≥85 years [126]. The reasons behind this, including reluctance by the elderly themselves, are complex and have been discussed by Petty *et al.* [127].

In a unique study of its kind, Wieringa *et al.* [128] have shown significant discrepancy between preregistration trials and postregistration use of cardiovascular drugs with regard to the representation of the elderly or the female cardiovascular patients. Clearly, much of the

information on which drugs are approved and used in the elderly is derived from studies involving younger adults. This lack of formal clinical trials in the elderly, and the apparent lack of efficacy and safety data, is thought to be a barrier to the optimal use of drugs in this population. The implication appears to be that efficacy, safety and risk–benefit of a given dose may be different in the elderly who are presumed to require lower doses because of age *per se*.

There has been an increasing trend recently towards greater representation of the elderly in a growing number of large-scale trials. These have supported the view that age *per se* in no way reduces the efficacy of drugs [129]. In a representative elderly cohort of patients with heart failure with systolic dysfunction, the majority (82%) were discharged on doses of ACE inhibitors consistent with those used in clinical trials. The investigators had observed a dose–response relationship between higher doses and lower mortality [130]. Even in elderly patients with perceived contraindication, ACE inhibitor use was associated with a significant survival benefit [131]. In one pharmacist-based pilot study of 48 octogenarians prescribed medications, 14 experienced undesirable effects while six had an inadequate effect [132]. This finding does not argue for a lower dose requirement in the elderly.

Compared with no β-blocker therapy, three different doses of β-blocker were all associated with lower adjusted risk ratio for mortality in the elderly – low dose 0.40, standard dose 0.36 and high doses 0.43 [133]. Although this finding supports the need for randomized controlled trials comparing a number of (lower) doses of β-blocker therapy, it is questionable if this need is unique to treatment of the elderly. The need to explore lower doses is general regardless of age. The notion that the elderly have low dose requirements because of age *per se* appears to have little scientific evidence. Age by itself is not a reason for withholding effective therapy.

This is not to deny that the risk–benefit ratio of a given intervention may be quite different in a population with significant comorbidities and/or comedication, including frail elderly patients. In another study, Wieringa *et al.* showed a discrepancy in the presence of comorbidity between the preapproval cardiovascular trials and that encountered in routine clinical practice [134]. Martin *et al.* confirmed the under-representation of the elderly and females in premarketing clinical trials but also extended their observations to show a similar discrepancy in the use of comedications [135]. Given this disproportionate excess of comorbidities and comedications in the elderly in routine clinical practice, it appears that these may account for the apparent differences in efficacy and safety between the elderly in routine clinical practice and their younger counterparts enrolled in clinical trials. Interestingly, a comparison of the patients who experienced ADRs with patients treated in the 'real world' did not identify any significant overrepresentation of a given characteristic that might act as a risk factor for ADR [135].

Even without the lack of formal efficacy and safety data from clinical trials in the elderly, the risk–benefit of medications in this population can be greatly improved by careful adherence to many basic therapeutic principles [84]. It is evident that age *per se* is not associated with significant changes in the pharmacokinetics of a drug. The changes that occur are the consequence of changes in hepatic or renal function, intake of food, comedications or pharmacogenetic influences. These can be anticipated and the dose of the drug adjusted. At a pharmacodynamic level, apart from a few pharmacological targets related to anticoagulants, cardiovascular and psychotropic drugs, there is at present little evidence that the majority of these targets display altered sensitivity in the elderly [136]. It seems probable that at least one concentration-controlled study in a small number of very elderly patients may provide sufficient data on age-related changes in pharmacodynamic susceptibility and help improve therapeutics in this age group. Kraiczi *et al.* have reviewed in detail the arguments for and against randomized concentration-controlled trials with regard to investigating pharmacokinetic and/or pharmacodynamic variability [137]. There is also an urgent need to examine the hypotheses of 'lower is better' and 'start low and go slow' as applied specifically to the elderly.

Determining the right dose in the frail elderly

Among 397 frail elderly inpatients, incorrect dosage was prescribed to 202 (50.9%) of the 365 patients with inappropriate use of medications. Duration of therapy was inappropriate in 187 (47.1%) patients. Furthermore, there was failure to consider drug–drug interactions in 25 (6.3%) patients and drug–disease interaction in a further 81 (20.4%) patients [4]. Prescribing patterns such as these render irrelevant the lack of formal clinical trials in the elderly as a major source of problems when determining the right dose in this population.

Although it is usual to study drug pharmacokinetics in the healthy elderly (usually those above 65 years of age), there is now a sound scientific rationale for studying frail elderly subjects and determining how drugs in this subgroup may interact with nutrition and nutritional status. Frail elderly persons are especially at risk

in relation to these food–drug interactions because they may accrue several risk factors (malnutrition, anorexia, alcoholism, chronic diseases, polypharmacy). Hitherto, clinical and pharmacological research in this area of gerontology has not attracted much attention. Very elderly will need better representation in future drug development programmes and the effect of frailty will almost certainly require investigation in frail elderly patients.

Conclusions

The main problems with prescribing drugs in the elderly during routine clinical practice arise from (a) the safety of drugs generally and the efficacy at the site of action – elderly patients may require a smaller number of receptors to be occupied than their younger counterparts. This difference in efficacy may mean that too high a dose is prescribed; (b) genetic influences; (c) duration of therapy; (d) drug–drug interactions; and (e) drug–disease interactions. Often, an incorrect dose is prescribed and there is little evidence to suggest that lack of clinical trials specifically in the elderly to investigate the effect of age *per se* is a major barrier to determining the right dose. Extrapolation of doses from clinical trials in younger adults (that may have excluded the elderly) to the elderly in routine clinical practice needs to be individualized on the basis of each patient's clinical and laboratory features and, if appropriate, the relevant genotype. There is an urgent need for better characterization of drug pharmacokinetic–pharmacodynamic relationships in the elderly, especially the very elderly and frail patients, and investigations concerning this are an important area in clinical pharmacology.

While it may be highly desirable to investigate different doses of every NCE in a formal efficacy trial in elderly patients, it is unlikely that a single study, however large, will address variability arising from all the covariates normally present in this age group. Rather than searching the 'right' dose for every drug from a large formal study in the elderly population with the notion that 'one size fits all', it is generally desirable and possible even in a clinical trial to determine an individualized dose appropriate to each elderly patient. These important decisions can be made from the data from pharmacokinetic studies in the elderly, effect of food, renal dysfunction, and hepatic dysfunction on the pharmacokinetics of the drug and drug–drug interaction studies. This applies especially to drugs that are primarily eliminated unchanged through renal excretion and have a narrow therapeutic index, e.g. digoxin.

In the final analysis, even if these data are not readily available and if drug therapy is considered beneficial or absolutely necessary, the dosage can easily be titrated to a clearly defined endpoint starting from a low initial dose [138, 139]. In the elderly, with complex interactions between polypharmacy, comorbidity, altered pharmacodynamic sensitivity and even modest changes in pharmacokinetics, there is much merit in this circumstance to a 'start low and go slow' approach.

Given the current interest in the role of pharmacogenetics in individualizing therapy, time has almost certainly come when genetic factors also need to be considered when developing and prescribing drugs to the elderly. Elderly patients who fail to respond as expected or those who unexpectedly develop adverse drug reactions should be appropriately genotyped.

More importantly, so spectacular are the results of advances in health and social care that one wonders if the time may have come to re-define the subset of population that constitutes 'the elderly population'. The outcome of these advances is a biological ageing process that lags far behind that of chronological ageing. The present criterion of an age over 65 years, established many years ago on the basis of changes in physiological functions and probably driven by the economically accepted age of retirement, is almost certainly outdated and needs to be reviewed, given the physical agility, psychological well-being, astute cognitive faculties, sexual drive and economic contribution of many who are currently designated 'the elderly'. Just as the paediatric population is categorized into infants and toddlers, children and adolescents (ICH guideline CPMP/ICH/2711/99) on the basis of age (and consequently body size) and the probable immaturity of processes responsible for absorption, distribution and elimination of drugs and of pharmacological targets, the time has come for similar re-categorization of the 'elderly' on the basis of age and consequent probability of decline in these functions. Since there is no sharp division in terms of biological changes with age, there is now a good case for re-defining the 'elderly' as those who are aged 75 years or more and the 'very elderly' as those who are aged 85 years or more. Since frailty can occur independently of age, the frail elderly constitute a unique subset in both these categories.

I wish to express my sincere appreciation to Professor Kenneth W. Woodhouse (University of Cardiff, UK) and to Professor Martin J. Kendall (University of Birmingham, UK) for their most helpful comments and constructive discussions during the preparation of this paper. Any deficiencies or shortcomings, however, are entirely my own responsibility.

References

1 Ahmed A, Allman RM, DeLong JF. Inappropriate use of digoxin in older hospitalized heart failure patients. J Gerontol a Biol Sci Med Sci 2002; 57: M138–M143.

2 Onder G, Landi F, Cesari M, Gambassi G, Carbonin P, Bernabei R. Inappropriate medication use among hospitalized older adults in Italy: results from the Italian Group of Pharmacoepidemiology in the Elderly. Eur J Clin Pharmacol 2003; 59: 157–62.

3 Onder G, Pedone C, Landi F et al. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc 2002; 50: 1962–8.

4 Hanlon JT, Artz MB, Pieper CF et al. Inappropriate medication use among frail elderly inpatients. Ann Pharmacother 2004; 38: 9–14.

5 Allen Maycock CA, Muhlestein JB, Horne BD et al. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. J Am Coll Cardiol 2002; 40: 1777–85.

6 Majumdar SR, Gurwitz JH, Soumerai SB. Undertreatment of hyperlipidemia in the secondary prevention of coronary artery disease. J General Intern Med 1999; 14: 711–17.

7 Williams D, Bennett K, Feely J. Evidence for an age and gender bias in the secondary prevention of ischaemic heart disease in primary care. Br J Clin Pharmacol 2003; 55: 604–8.

8 DeWilde S, Carey IM, Bremner SA, Richards N, Hilton SR, Cook DG. Evolution of statin prescribing 1994–2001: a case of agism but not of sexism? Heart 2003; 89: 417–21.

9 Berlowitz DR, Ash AS, Hickey EC et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med 1998; 339: 1957–63.

10 Landi F, Cesari M, Onder G et al. Antithrombotic drugs in secondary stroke prevention among a community dwelling older population. J Neurol Neurosurg Psychiatry 2003; 74: 1100–4.

11 McCormick D, Gurwitz JH, Goldberg RJ et al. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. Arch Intern Med 2001; 161: 2458–63.

12 Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. JAMA 1997; 277: 115–21.

13 Heller DA, Ahern FM, Kozak M. Changes in rates of beta-blocker use between 1994 and 1997 among elderly survivors of acute myocardial infarction. Am Heart J 2000; 140: 663–71.

14 Ahmed A, Allman RM, DeLong JF, Bodner EV, Howard G. Age-related underutilization of angiotensin-converting enzyme inhibitors in older hospitalized heart failure patients. South Med J 2002; 95: 703–10.

15 Havranek EP, Abrams F, Stevens E, Parker K. Determinants of mortality in elderly patients with heart failure: the role of angiotensin-converting enzyme inhibitors. Arch Intern Med 1998; 158: 2024–8.

16 Jackson SHD, Mangoni AA, Batty GM. Optimization of drug prescribing. Br J Clin Pharmacol 2004; 57: 231–6.

17 Simon SR, Gurwitz JH. Drug therapy in the elderly: improving quality and access. Clin Pharmacol Ther 2003; 73: 387–93.

18 Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002; 288: 455–61.

19 Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002; 288: 462–7.

20 Butler J, Arbogast PG, BeLue R et al. Outpatient adherence to beta-blocker therapy after acute myocardial infarction. J Am Coll Cardiol 2002; 40: 1589–95.

21 Kamal A, Koch IM. Pharmacokinetic studies of benoxaprofen in geriatric patients. Eur J Rheumatol Inflamm 1982; 5: 76–81.

22 Hamdy RC, Murnane B, Perera N, Woodcock K, Koch IM. The pharmacokinetics of benoxaprofen in elderly subjects. Eur J Rheumatol Inflamm 1982; 5: 69–75.

23 Nash JF, Carmichael RH, Ridolfo AS, Spradlin CT. Pharmacokinetic studies of benoxaprofen after therapeutic doses with a review of related pharmacokinetic and metabolic studies. J Rheumatol 1980; 6 (Suppl.): 12–9.

24 Brogard JM, Comte F, Madon M, Spach MO. Pharmacokinetic profile of benoxaprofen in subjects with normal and impaired renal function, prediction of multiple-dose kinetics. Eur J Rheumatol Inflamm 1982; 5: 113–23.

25 Aronoff GR, Ozawa T, DeSante KA, Nash JF, Ridolfo AS. Benoxaprofen kinetics in renal impairment. Clin Pharmacol Ther 1982; 32: 190–4.

26 Hallén B, Bogentoft S, Sandquist S, Strömberg S, Setterberg G, Ryd-Kjellén E. Tolerability and steady-state pharmacokinetics of terodiline and its main metabolites in elderly patients with urinary incontinence. Eur J Clin Pharmacol 1989; 36: 487–93.

27 Woodhouse KW. Pharmacokinetics of drugs in the elderly. J R Soc Med 1994; 87 (Suppl. 23): 2–4.

28 Beyth RJ, Shorr RI. Epidemiology of adverse drug reactions in the elderly by drug class. Drugs Aging 1999; 14: 231–9.

29 Forbes GB, Reina JC. Adult lean body mass declines with age; some longitudinal observations. Metabolism 1970; 19: 653–63.

30 O'Mahony MS. Pharmacokinetics. In Drugs and Older Population, Chapter 4, eds Crome P, Ford G. London: Imperial College Press, 2000: 58–89.

31 Greenblatt DJ. Reduced serum albumin concentrations in the elderly: a report from Boston Collaborative Drug Surveillance Program. J Am Geriatr Soc 1979; 27: 20–2.

32 Abernethy DR, Kerzner L. Age effects on alpha1-acid glycoprotein concentration and imipramine plasma protein binding. J Am Geriatr Soc 1984; 32: 705–8.

33 Koyama H, Mori S, Sugioka N, Nishihara T, Nakajima K. Age-related alteration of haloperidol-serum protein binding. J Pharm Pharmacol 2003; 55: 77–83.

34 Brenner SS, Herrlinger C, Dilger K et al. Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition

of diclofenac and celecoxib. Clin Pharmacokinet 2003; 42: 283–92.

35 Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther 1997; 61: 331–9.

36 Woodhouse KW, James OFW. Hepatic drug metabolism and ageing. Br Med Bull 1990; 46: 22–35.

37 Wynne HA, Goudevenos J, Rawlins MD, James OFW, Adams PC, Woodhouse KW. Hepatic drug clearance: the effect of age using indocyanine green as a model compound. Br J Clin Pharmacol 1990; 30: 634–7.

38 Tanaka E. Clinical importance of non-genetic and genetic cytochrome P450 function tests in liver disease. J Clin Pharm Ther 1998; 23: 161–70.

39 Yang LQ, Li SJ, Cao YF et al. Different alterations of cytochrome P450 3A4 isoform and its gene expression in livers of patients with chronic liver diseases. World J Gastroenterol 2003; 9: 359–63.

40 Lanthier PL, Reshef R, Shah RR, Oates NS, Smith RL, Morgan MY. Oxidation phenotyping in alcoholics with liver disease of varying severity. Alcohol Clin Exp Res 1984; 8: 435–41.

41 Adedoyin A, Arns PA, Richards WO, Wilkinson GR, Branch RA. Selective effect of liver disease on the activities of specific metabolizing enzymes: investigation of cytochrome P450 2C19 and 2D6. Clin Pharmacol Ther 1998; 64: 8–17.

42 Abou-Hatab K, Ganeshalingam K, O'Mahony MS, Giurani F, Patel S, Woodhouse K. The effect of community-acquired pneumonia on plasma esterases in older people. Eur J Clin Pharmacol 2001; 57: 55–60.

43 O'Mahony MS, George G, Westlake H, Woodhouse K. Plasma aspirin esterase activity in elderly patients undergoing elective hip replacement and with fractured neck of femur. Age Ageing 1994; 23: 338–41.

44 Rowe JW, Andres R, Tobin JD. Age-adjusted standards for creatinine clearance. Ann Intern Med 1976; 84: 567–9.

45 Dreisbach AW, Lertora JJ. The effect of chronic renal failure on hepatic drug metabolism and drug disposition. Semin Dial 2003; 16: 45–50.

46 Guevin C, Michaud J, Naud J, Leblond FA, Pichette V. Down-regulation of hepatic cytochrome P450 in chronic renal failure: role of uremic mediators. Br J Pharmacol 2002; 137: 1039–46.

47 Pichette V, Leblond FA. Drug metabolism in chronic renal failure. Curr Drug Metab 2003; 4: 91–103.

48 Kim YG, Shin JG, Shin SG et al. Decreased acetylation of isoniazid in chronic renal failure. Clin Pharmacol Ther 1993; 54: 612–20.

49 Dowling TC, Briglia AE, Fink JC et al. Characterization of hepatic cytochrome P4503A activity in patients with end-stage renal disease. Clin Pharmacol Ther 2003; 73: 427–34.

50 Rostami-Hodjegan A, Kroemer HK, Tucker GT. In-vivo indices of enzyme activity: the effect of renal impairment on the assessment of CYP2D6 activity. Pharmacogenetics 1999; 9: 277–86.

51 Dreisbach AW, Japa S, Gebrekal AB et al. Cytochrome P4502C9 activity in end-stage renal disease. Clin Pharmacol Ther 2003; 73: 475–7.

52 Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. Biochem Pharmacol 1992; 44: 275–83.

53 Hammerlein A, Derendorf H, Lowenthal DT. Pharmacokinetic and pharmacodynamic changes in the elderly. Clinical implications. Clin Pharmacokinet 1998; 35: 49–64.

54 Vuyk J. Pharmacodynamics in the elderly. Best Pract Res Clin Anaesthesiol 2003; 17: 207–18.

55 McGeer PL, McGeer EG, Suzuki J, Dolman CE, Nagai T. Aging, Alzheimer's disease and the cholinergic system of the basal forebrain. Neurology 1984; 34: 741–5.

56 Joseph JA, Berger RE, Engle BT, Roth GS. Age-related changes in the nigrostriatum: a behavioral and biochemical analysis. J Gerontol 1978; 33: 643–9.

57 Morgan DG, May PC, Finch CE. Dopamine and serotonin systems in human and rodent brain: effects of age and neurodegenerative disease. J Am Geriatr Soc 1987; 35: 334–45.

58 Robinson DS, Nies A, Davis JM et al. Aging, monoamines, and monoamine oxidase levels. Lancet 1972; 1: 290–1.

59 Bertier A. Occurrence and localization of catecholamines in the human brain. Acta Physiol Scand 1961; 51: 97–107.

60 Vestal RE, McGuire EA, Tobin JD, Andres R, Norris AH, Mezey E. Aging and ethanol metabolism. Clin Pharmacol Ther 1977; 21: 343–54.

61 Arranz B, Eriksson A, Mallerup E, Plenge P, Marcusson J. Effect of aging in human cortical pre- and postsynaptic serotonin binding sites. Brain Res 1993; 620: 163–6.

62 Vestal RE, Wood AJ, Shand DG. Reduced β-adrenoceptor sensitivity in the elderly. Clin Pharmacol Ther 1979; 26: 181–6.

63 Ritchie CW, Chiu E, Harrigan S et al. The impact upon extra-pyramidal side effects, clinical symptoms and quality of life of a switch from conventional to atypical antipsychotics (risperidone or olanzapine) in elderly patients with schizophrenia. Int J Geriatr Psychiatry 2003; 18: 432–40.

64 Reardon M, Malik M. QT interval change with age in an overtly healthy older population. Clin Cardiol 1996; 19: 949–52.

65 Daly AK. Pharmacogenetics of the major polymorphic metabolizing enzymes. Fundam Clin Pharmacol 2003; 17: 27–41.

66 Daly AK, King BP. Pharmacogenetics of oral anticoagulants. Pharmacogenetics 2003; 13: 247–52.

67 Verstuyft C, Robert A, Morin S et al. Genetic and environmental risk factors for oral anticoagulant overdose. Eur J Clin Pharmacol 2003; 58: 739–45.

68 Loebstein R, Yonath H, Peleg D et al. Interindividual variability in sensitivity to warfarin – nature or nurture? Clin Pharmacol Ther 2001; 70: 159–64.

69 Price-Evans DA, Mahgoub A, Sloan TP, Idle JR, Smith RL. A family and population study of the genetic polymorphism of

debrisoquine oxidation in a British white population. J Med Genet 1980; 17: 102–5.

70 Dahl ML, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. J Pharmacol Exp Ther 1995; 274: 516–20.

71 Lovlie R, Daly AK, Matre GE, Molven A, Steen VM. Polymorphisms in CYP2D6 duplication-negative individuals with the ultrarapid metabolizer phenotype: a role for the CYP2D6*35 allele in ultrarapid metabolism? Pharmacogenetics 2001; 11: 45–55.

72 Yamada H, Dahl ML, Lannfelt L, Viitanen M, Winblad B, Sjoqvist F. CYP2D6 and CYP2C19 genotypes in an elderly Swedish population. Eur J Clin Pharmacol 1998; 54: 479–81.

73 Lima JJ, Thomason DB, Mohamed MH, Eberle LV, Self TH, Johnson JA. Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. Clin Pharmacol Ther 1999; 65: 519–25.

74 Israel E, Drazen JM, Liggett SB et al. Effect of polymorphism of the beta2-adrenergic receptor on response to regular use of albuterol in asthma. Int Arch Allergy Immunol 2001; 124: 183–6.

75 Drazen JM, Yandava CN, Dube L et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. Nat Genet 1999; 22: 168–70.

76 Liggett SB, Wagoner LE, Craft LL et al. The Ile164 beta2-adrenergic receptor polymorphism adversely affects the outcome of congestive heart failure. J Clin Invest 1998; 102: 1534–9.

77 Wagoner LE, Craft LL, Zengel P et al. Polymorphisms of the beta1-adrenergic receptor predict exercise capacity in heart failure. Am Heart J 2002; 144: 840–6.

78 Borjesson M, Magnusson Y, Hjalmarson A, Andersson B. A novel polymorphism in the gene coding for the beta1-adrenergic receptor associated with survival in patients with heart failure. Eur Heart J 2000; 21: 1853–8.

79 Weizman A, Weizman R. Serotonin transporter polymorphism and response to SSRIs in major depression and relevance to anxiety disorders and substance abuse. Pharmacogenomics 2000; 1: 335–41.

80 Smeraldi E, Zanardi R, Benedetti F, Di Bella D, Perez J, Catalano M. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998; 3: 508–11.

81 Kim DK, Lim SW, Lee S et al. Serotonin transporter gene polymorphism and antidepressant response. Neuroreport 2000; 11: 215–9.

82 Murphy GM, Kremer C, Rodrigues HE, Schatzberg AF. Pharmacogenetics of antidepressant medication intolerance. Am J Psychiatr 2003; 160: 1830–5.

83 Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. Ann Intern Med 1991; 114: 956–66.

84 Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol 2004; 57: 121–6.

85 Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 1993; 270: 2590–7.

86 Shah RR. Drug-induced hepatotoxicity: pharmacokinetic perspectives and strategies for risk reduction. Adverse Drug React Toxicol Rev 1999; 18: 181–233.

87 Ahmad SR, Kortepeter C, Brinker A, Chen M, Beitz J. Renal failure associated with the use of celecoxib and rofecoxib. Drug Saf 2002; 25: 537–44.

88 Beardon PHG, Brown SV, McDevitt DG. Gastrointestinal events in patients prescribed non-steroidal anti-inflammatory drugs: a controlled study using record linkage in Tayside. Q J Med 1989; 71: 497–505.

89 Griffin MR, Piper JM, Daughtery K, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991; 114: 257–63.

90 Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000; 160: 2093–9.

91 Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther 2004; 11: 17–25.

92 Sibilia J, Ravaud P, Marck G. Risk factors for gastrointestinal bleeding associated with low-dose aspirin [in French]. Presse Med 2003; 32 (37 Part 2): S9–S16.

93 Pilotto A, Franceschi M, Leandro G, Di Mario F, Geriatric Gastroenterology Study Group (Societe Italiana Gerontologie Geriatria). NASID and aspirin use by the elderly in general practice: effect on gastrointestinal symptoms and therapies. Drugs Aging 2003; 20: 701–10.

94 Lanas A, Ferrandez A. Treatment and prevention of aspirin-induced gastroduodenal ulcers and gastrointestinal bleeding. Expert Opin Drug Saf 2002; 1: 245–52.

95 Scapa E, Horowitz M, Waron M, Eshchar J. Duodenal ulcer in the elderly. J Clin Gastroenterol 1989; 11: 502–6.

96 Jankel CA, Speedie SM. Detecting drug interactions: a review of the literature. DICP Ann Pharmacother 1990; 24: 982–9.

97 Doucet J, Chassagne P, Trivalle C et al. Drug–drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients. J Am Geriatr Soc 1996; 44: 944–8.

98 Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug–drug interactions among elderly patients hospitalised for drug toxicity. JAMA 2003; 289: 1652–8.

99 Shah RR. Mechanistic basis of adverse drug reactions: the perils of inappropriate dose schedules. Exp Opin Drug Saf 2004; in press.

100 Roe CM, Odell KW, Henderson RR. Concomitant use of antipsychotics and drugs that may prolong the QT interval. J Clin Psychopharmacol 2003; 23: 197–200.

101 Curtis LH, Ostbye T, Sendersky V et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. Am J Med 2003; 114: 135–41.

102 Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 2001; 96: 1698–703.

103 Kiivet RA, Llerena A, Dahl ML et al. Patterns of drug treatment of schizophrenic patients in Estonia, Spain and Sweden. Br J Clin Pharmacol 1995; 40: 467–76.

104 Procyshyn RM, Kennedy NB, Tse G, Thompson B. Antipsychotic polypharmacy: a survey of discharge prescriptions from a tertiary care psychiatric institution. Can J Psychiatry 2001; 46: 334–9.

105 Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 2000; 51: 245–70.

106 Bruunsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. Immunol Allergy Clin North Am 2003; 23: 15–39.

107 Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol a Biol Sci Med Sci 2001; 56: M146–M156.

108 Ferrucci L, Guralnik JM, Cavazzini C et al. The frailty syndrome: a critical issue in geriatric oncology. Crit Rev Oncol Hematol 2003; 46: 127–37.

109 Ranieri P, Rozzini R, Franzoni S, Barbisoni P, Trabucchi M. Serum cholesterol levels as a measure of frailty in elderly patients. Exp Aging Res 1998; 24: 169–79.

110 de Jong N, Chin A, Paw MJ et al. Functional biochemical and nutrient indices in frail elderly people are partly affected by dietary supplements but not by exercise. J Nutr 1999; 129: 2028–36.

111 Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum albumin level and physical disability as predictors of mortality in older persons. JAMA 1994; 272: 1036–42.

112 Chevalier S, Gougeon R, Nayar K, Morais JA. Frailty amplifies the effects of aging on protein metabolism: role of protein intake. Am J Clin Nutr 2003; 78: 422–9.

113 Wynne HA, Cope LH, Herd B, Rawlins MD, James OF, Woodhouse KW. The association of age and frailty with paracetamol conjugation in man. Age Ageing 1990; 19: 419–24.

114 Williams FM, Wynne H, Woodhouse KW, Rawlins MD. Plasma aspirin esterase: the influence of old age and frailty. Age Ageing 1989; 18: 39–42.

115 Summerbell J, Yelland C, Woodhouse K. The kinetics of plasma aspirin esterase in relation to old age and frailty. Age Ageing 1990; 19: 128–30.

116 Hughes KM, Lang JC, Lazare R et al. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica 1992; 22: 859–69.

117 Wynne HA, Yelland C, Cope LH, Boddy A, Woodhouse KW, Bateman DN. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. Age Ageing 1993; 22: 354–9.

118 Carpino PA, Lefker BA, Toler SM et al. Pyrazolinone-piperidine dipeptide growth hormone secretagogues (GHSs). Discovery of capromorelin. Bioorg Med Chem 2003; 11: 581–90.

119 Pickering G. Frail elderly, nutritional status and drugs. Arch Gerontol Geriatr 2004; 38: 174–80.

120 Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 2000; 356: 1667–71.

121 Sallustio BC, Westley IS, Morris RG. Pharmacokinetics of the antianginal agent perhexiline: relationship between metabolic ratio and steady-state dose. Br J Clin Pharmacol 2002; 54: 107–14.

122 Kirchheiner J, Brosen K, Dahl ML et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand 2001; 104: 173–92.

123 Evelyn B, Toigo T, Banks D et al. Participation of racial/ethnic groups in clinical trials and race-related labeling: a review of new molecular entities approved 1995–1999. J Natl Med Assoc 2001; 93 (Suppl. 12): 18S–24S.

124 Cross J, Lee H, Westelinck A, Nelson J, Grudzinskas C, Peck C. Postmarketing drug dosage changes of 499 FDA-approved new molecular entities, 1980–1999. Pharmacoepidemiol Drug Safety 2002; 11: 439–46.

125 Cohen JS. Dose discrepancies between the Physicians' Desk Reference and the medical literature, and their possible role in the high incidence of dose-related adverse drug events. Arch Intern Med 2001; 161: 957–64.

126 Rochon PA, Fortin PR, Dear KB, Minaker KL, Chalmers TC. Reporting of age data in clinical trials of arthritis. Deficiencies and solutions. Arch Intern Med 1993; 153: 243–8.

127 Petty DR, Zermansky AG, Raynor DK et al. 'No thank you': why elderly patients declined to participate in a research study. Pharm World Sci 2001; 23: 22–7.

128 Wieringa NF, de Graeff PA, van der Werf GT, Vos R. Cardiovascular drugs: discrepancies in demographics between pre- and post-registration use. Eur J Clin Pharmacol 1999; 55: 537–44.

129 Swift CG. The clinical pharmacology of ageing. Br J Clin Pharmacol 2003; 56: 249–53.

130 Chen YT, Wang Y, Radford MJ, Krumholz HM. Angiotensin-converting enzyme inhibitor dosages in elderly patients with heart failure. Am Heart J 2001; 141: 410–7.

131 Ahmed A, Kiefe CI, Allman RM, Sims RV, DeLong JF. Survival benefits of angiotensin-converting enzyme inhibitors in older heart failure patients with perceived contraindications. J Am Geriatr Soc 2002; 50: 1659–66.

132 Seevak E, Kent DJ, Wagner E. A pharmacist-based screening program of octogenarians starting new medications. J Manag Care Pharm 2003; 9: 13–8.

133 Rochon PA, Tu JV, Anderson GM et al. Rate of heart failure and 1-year survival for older people receiving low-dose beta-

blocker therapy after myocardial infarction. Lancet 2000; 356: 639–44.

134 Wieringa NF, Vos R, van der Werf GT, van der Veen WJ, de Graeff PA. Co-morbidity of 'clinical trial' versus 'real-world' patients using cardiovascular drugs. Pharmacoepidemiol Drug Safety 2000; 9: 569–79.

135 Martin K, Begaud B, Latry P, Miremont-Salame G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J Clin Pharmacol 2004; 57: 86–92.

136 Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principals and practical applications. Br J Clin Pharmacol 2004; 57: 6–14.

137 Kraiczi H, Jang T, Ludden T, Peck CC. Randomized concentration-controlled trials: motivations, use, and limitations. Clin Pharmacol Ther 2003; 74: 203–14.

138 Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol 2003; 38: 843–53.

139 Rehman HU, Han S. Pharmacotherapy in old age. J R Coll Physicians Edin 2004; 34: 21–7.