MEDICATION

IN THE

ELDERLY:

AN OUTPATIENT SURVEY

—

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August 1987

Doctors pour drugs,
of which they know very little,
into patients,
of whom they know even less.

Voltaire

The use of drugs,
like the application of diplomacy,
is the art of the possible

Freeman

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ACKNOWLEDGEMENTS

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My wife Jenny, our children, and our parents, tolerated my commitment to this project with remarkable patience - their support was of great value to me.

A work such as this is not produced in isolation: I acknowledge with gratitude the assistance received from many people, especially the staff of the General Out-patient Department at Groote Schuur Hospital, the Medical Records Department, and the Medical School Library. Mr. Walter Kahn of Maynards, Cape Town, gave me valuable advice on the use of the computer on which this document was produced.

Our patients help teach us about medicine, and this study is no exception. It is my hope that this work will ultimately be of benefit to them.

Cape Town,
August 1987

Signed by candidate

C K DAVIS

ABSTRACT

The aging process is associated with disease states that may be painful, disabling and life-threatening. Elderly patients frequently have more than one disorder and appropriate pharmacotherapy may result in polypharmacy (treatment with multiple drugs). This situation, combined with age-related alterations in the handling of and sensitivity to drugs, predisposes older patients to adverse drug reactions (ADR's).

This study was undertaken to assess the actual risks and potential benefits of long-term polypharmacy in the management of elderly hospital out-patients. A particular aim was to get some indication of whether or not polypharmacy was justifiable in the study population. Accordingly the medical records of 132 ambulatory patients, 70 years of age and over, who had been attending the general out-patient department of a large teaching hospital for a period of twelve months or longer, were retrospectively examined. The patient's age, diagnoses, prescribed medication, ADR's and clinical therapeutic benefit were assessed, recorded and analyzed.

The average patient age in the sample studied was 77,6 years. 71% of the sample were females. 419 disorders were identified, giving an average of 3,17 per patient. 603 drugs

were prescribed in total, giving an average of 4,57 per patient. There was no statistically significant association between increasing age and the number of diagnoses per patient or the number of drugs prescribed. Medication was felt to be therapeutically effective in 63% of the patients, whilst an ADR was noted in 14% of the sample. There was no statistically significant difference in the age, number of diseases or number of drugs prescribed between the total group, the ADR group and the non-ADR group. These parameters were therefore not useful in identifying those patients more likely to experience an ADR.

The apparent effectiveness of the medication prescribed and the relatively low incidence of ADR's in the group studied suggests that appropriate and judicious multiple drug therapy can benefit many elderly ambulatory patients and therefore polypharmacy could be regarded as permissible in this context. Apart from these observations, this dissertation also includes recommendations on ways to minimize the incidence of ADRs in the elderly, and areas for ongoing research in this field are identified.

CHAPTER ONE

DRUGS AND THE ELDERLY

As people age they tend to acquire conditions which can be painful, disabling and even life-threatening. In attempting to help older people, health professionals often prescribe medication which may be both efficacious and safe, but at other times may do more harm than good. Epidemiological data and pharmacological studies in the aged have shown that drugs are used more frequently in the elderly, whilst their therapeutic and adverse reaction profile tends to differ from that found in younger patients.

Pharmacological considerations

The nature of the primary aging process has yet to be defined, but it is accompanied by physiological changes and age-related diseases.[1] These in turn may profoundly alter patient response to therapy, but this is difficult to predict due to the increase in interpatient variability that occurs with age.[2] Associated alterations in the absorption, distribution, metabolism and elimination of drugs (pharmacokinetics) are among the major factors that

contribute to the potential toxicity of certain drugs in the elderly.[3]

The absorption of drugs in the elderly may be influenced by decreased gastric acid production, delayed gastric emptying, diminished splanchnic blood flow, and reduced gastro-intestinal mucosal cell mass. These changes however appear to be of little clinical significance.[4]

The distribution of drugs can be altered as a result of the reduced lean body mass, reduced total body water, and increased total body fat found in the elderly. Thus, generally speaking, the distribution of hydrophilic drugs (such as paracetamol) tends to decrease in the elderly, whilst that of lipophilic drugs (such as diazepam) tends to increase. This can result in clinically important changes in drug half-lives and serum drug concentrations.[5]

Another important determinant of drug distribution in the elderly is a reduced serum albumin concentration.[6] Mild reductions in serum albumin may be present in healthy older patients, but those who are chronically ill or malnourished may have substantial reductions. These changes are important when highly protein-bound drugs are used, as a low albumin decreases the number of available binding sites which in turn increases the amount of free (active) drug. Many drugs (such as warfarin, nonsteroidal anti-inflammatory

drugs, diazepam and phenytoin) compete for the available albumin binding sites, and in the elderly there is considerable potential for interaction between drugs due to the displacement of one by another, leading to increased serum concentration of the displaced free drug and resultant toxicity. The acidic drugs are the agents most involved in such displacement reactions.

Age-related changes in liver function may affect the metabolism of certain drugs.[4] Liver mass falls with advancing age, and liver blood flow may also decrease with increasing age. For orally administered lipid soluble drugs with a high hepatic elimination rate (such as propanolol and verapamil), these factors may result in reduced first pass metabolism and thus increased bio-availibility. Hepatic biotransformation reactions such as oxidation, reduction, or hydrolysis (Phase I) may be significantly impaired in older patients. For certain of the hepatically metabolized benzodiazepines, notably diazepam and chlordiazepoxide, impairment of oxidative reactions appears to be greatest in elderly men. Hepatic conjugation reactions (Phase II) do not appear to alter significantly with advancing age. The contribution of aging to altered hepatic drug metabolism is in any event confounded by other variables such as inter-individual genetic variation, nutritional and vitamin status, caffeine and cigarette consumption, and cardiac output.

An important pharmacokinetic cause of adverse drug reactions in the elderly is impaired renal function.[6] Renal plasma flow decreases gradually from 600 ml/min in the second decade of life to 300 ml/min in the eighth decade, and there are also reductions in the glomerular filtration rate. However, wide variation in the rates of decline with aging in individual persons is seen. Renal circulation and function is furthermore often particularly sensitive in the elderly to extrarenal factors such as disease and drugs, thus compounding the above changes. Impaired renal function results in impaired elimination of those drugs excreted by glomerular filtration (such as digoxin and cimetidine) and those excreted by tubular secretion (such as the penicillins, cephalosporins and aminoglycosides).

The ability to measure certain drug levels has made it relatively easy to study drug disposition in the elderly. Of equal importance are the effects of a given concentration of drug at its site of action (pharmacodynamics) but this has been less studied in man because of the considerable difficulties involved. However it has been shown that the elderly are more resistant to the effects of isoprenaline and propanolol and more sensitive to certain of the benzodiazepines and warfarin.[3] Much additional research is needed to further characterize age-related alterations in pharmacodynamics.

Epidemiological data

It has been estimated that over 15 million elderly Americans have one or more chronic illnesses, this presumably accounting in part for the fact that in the U.S.A. 25 to 30 percent of total drug expenditure represents medication for the elderly, who make up only 11 percent of the population.[7] Although corresponding data for the situation in South Africa are not available[8], the number of elderly in this country should increase dramatically in the next decade.[9]

Recent data from the United States indicates that 12 to 17 percent of all hospital admissions of elderly patients are due to adverse drug effects, which is three to four times the rate for all other patients.[10] The cost of adverse drug reactions in the elderly may well approach three billion dollars a year.[10] A study in the United Kingdom involving 2 000 admissions to 42 Geriatric Units has shown that about ten percent of all patients were admitted solely or partly because of adverse drug reactions.[11] As far as is known, there has only been one report from South Africa of hospital admissions related to adverse drug reactions (ADRs).[12] The study found that 4,6% of all admissions were ADR related, and all the affected patients were over 50 years of age, with a median age of 73 years. Other data suggests that adverse reactions to drugs increase progressively from about thirty years of age onwards, with a particularly noticeable increase

after the age of 65,[13] and the frequency of adverse drug effects among community-living elderly may be as high as 40 percent.[14]

Although the above-mentioned studies provide reasons for concern about the problem of ADRs among the elderly, it has been suggested that many such studies have either methodological weaknesses or are prone to misinterpretation.[15] Another report has stated that "the data on ADRs are incomplete, unrepresentative, uncontrolled, and lacking in operational criteria for identifying ADRs."[16] The authors were particularly concerned about the fact that the great majority of the available reports are based on hospitalised patients in acute medical wards. Such patients may differ considerably from the ambulatory patients who account for the bulk of medicinal use.

It was with these factors in mind that the study described in this report was undertaken. The purpose and methodology are described in the following chapter.

CHAPTER TWO

AN OUTPATIENT SURVEY AT GROOTE SCHUUR HOSPITAL

Despite the fact that the elderly are an at-risk group for adverse drug reactions, they are frequently treated with multiple medications for multiple ailments, resulting in a situation which has become known as polypharmacy.[17] This is perceived as a problem by many health care professionals and administrators, primarily because of the possible morbidity, mortality, and resultant financial costs that may occur when multiple drug therapy is used. However it may also be a necessity, given the variety and number of symptomatic disorders that the elderly are prone to, and the problem of polypharmacy may therefore only be of relevance where unnecessary or inappropriate drugs are prescribed, or where indicated drugs are used incorrectly, or where the prescriber does not watch for toxicity. It has been stated that "polypharmacy (in the elderly) is not only inevitable, but to insist on its rigid control to predetermined numbers of items by arbitrary decision could be a negation of good medicine and inhumane."[18]

The study described in this dissertation was undertaken to assess whether, in the typical setting provided by an outpatient clinic of a major teaching hospital, combinations of drugs could be prescribed to the elderly over a reasonable period of time without the emergence of an unduly high incidence of side-effects. Furthermore, in order to properly evaluate polypharmacy, an attempt was made to simultaneously aseess the efficacy of the drugs being used. Folb has stated that "a risk-benefit assessment has to be made by the physician in prescribing any medicine. It is a challenge to all concerned that the physician is fully informed as to both sides of that equation."[19]

Methods

A consecutive series of the medical records of patients aged 70 and over who had attended the white General Out-patient Department (GOPD) at Groote Schuur Hospital from 1 June 1982 onwards was used in this study. At the time of the study, many elderly pensioners attended GOPD for initial and ongoing assessment and medication. The medical staff of GOPD consisted mainly of senior General Practitioners. It was felt that this situation was one in which polypharmacy in the elderly could be studied.

The patient population was considered to be homogenous as regards its general characteristics, and for this reason the

consecutive series used was felt to be representative of the population studied and so no further randomization was done. As this study was concerned with the efficacy and safety of long-term polypharmacy, only the records of those patients who had been attending GOPD for a period of 12 months or longer were used. However, in screening the records of patients who had been attending for less than twelve months, there was no evidence that these patients experienced a higher or lower incidence of side-effects than those who had been attending for longer. In all, during the time available for the study, the records of 132 patients who fulfilled the above criteria were retrospectively examined and analysed by the author. A formatted data collection sheet was used (Appendix I) with information being recorded in the following classes:

i) Patient age and sex;

ii) Number of disorders being treated;

iii) Drugs prescribed for each patient, and dosage;

iv) Length of time (in months) that the patient had been on the identical prescription;

v) If there had been any stop or change in medication since the start of the patient's attendance at GOPD, the reason/s for this were noted: e.g. emergence of side-effects, therapeutic failure, appearance of an additional disorder;

vi) If side-effects had been noted in (v), the drugs responsible were recorded and also any possible interaction between drugs;

vii) Any indication in the medical record that the current prescription appeared effective in controlling the symptoms or natural history of the disorder being treated. This is explained in more detail on page 13.

Limitations of the methods used

Data collection in classes (i) to (iv) was done by simply recording available data from the patient's hospital folder. However at least one study[20] has shown that there are often considerable discrepancies between the number and types of drugs recorded in the hospital record and the drugs that the patient is actually taking. In that study, a review of the actual medication being taken by the patient showed that 16 per cent were making some major error or omission when the drugs were compared with those listed in their hospital file.

The other problem in a retrospective study of this nature is that parameters such as drug efficacy or side-effects may not be recorded as such in the patient's folder and thus may have to be assessed by the observer from the clinical notes. This is subject to observer bias and difficulties and errors in interpretation.[21] This kind of problem was illustrated in one study of presumably healthy individuals who were not on medication, where 81 per cent of respondents reported having experienced symptoms during the 72 hour period before questioning that could have been classified as adverse drug reactions.[22] The World Health Organisation's definition of an adverse drug reaction (ADR) as: "Any response to a drug which is noxious and unintended and which occurs in doses in man for prophylaxis, diagnosis, or therapy" requires observer interpretation of noxiousness.[23]

The other problem in the assessment of ADR's is the establishment of a causal role between an adverse event and a drug, particularly in the presence of polypharmacy. This has led to the redefinition of an ADR as "an undesirable clinical manifestation consequent to and caused by the administration of a given drug"[24], and since this definition includes the concepts of noxiousness and causality, it was used in this study. However defining causality in the clinical setting is largely dependent on an experienced observer, and in an attempt to improve validity and reproducibilty, an algorithm has been developed to assess the

causal association between drug and event.[24] This algorithm rates the probability of causality by incorporating issues such as the previous general experience with the drug, alternative aetiological candidates, timing of events, drug levels, evidence of overdose, and dechallenge and rechallenge. However at least one study has concluded that, when compared to informal assessment by one observer alone, the use of such algorithms in drug surveillance programs "does not improve the uniformity (or validity) of adverse drug reaction assessments."[25]

Despite difficulties with methods of causality assessment for suspected ADRs,[26] the author's experience in presribing for many elderly patients has been that frequently patients give remarkably good accounts of untoward symptoms that they can clearly attribute to a given drug. The ADR's recorded in our study were either spontaneously reported by the patient, or noted by the attending physician in assessing a symptom or physical sign.

The assessment of efficacy is in many ways subject to similar diificulties that have been discussed above regarding the detection and interpretation of ADR's. Spilker has stated that "many efficacy measures yield less objective data than one would ideally like to obtain. Subjective measures often depend on clinical evaluation or examination of the patient or on the investigator's interpretation of the patient's

statements. Under these circumstances, it is generally desirable to have the same investigator perform the nonobjective measures throughout the study."[27]

As this study was retrospective, use had to be made of subjective measures of efficacy, as assessed by the author when reviewing the clinical records. Treatment was judged as effective if follow-up notes contained a statement such as "feels much better", or if the physical signs for which the medication was being given had responded favourably (e.g. reduction in blood pressure). Treatment was regarded as ineffective if the original problem had persisted unchanged. If there was no evidence either way, efficacy was recorded as uncertain. The assessment of efficacy in this study was thus problematic, mainly because of the potential for observer bias on the part of the patient, the attending physician and the author. It was nevertheless undertaken as part of the overall analysis of polypharmacy in the study group, whilst the findings have to be interpreted with the above limitations in mind.

Data analysis

Data from the data collection sheets was entered into the Cracker-II graphical spreadsheet[28] and this was processed on an Amstrad PCW8256. The results are detailed in the following chapter.

CHAPTER THREE

RESULTS

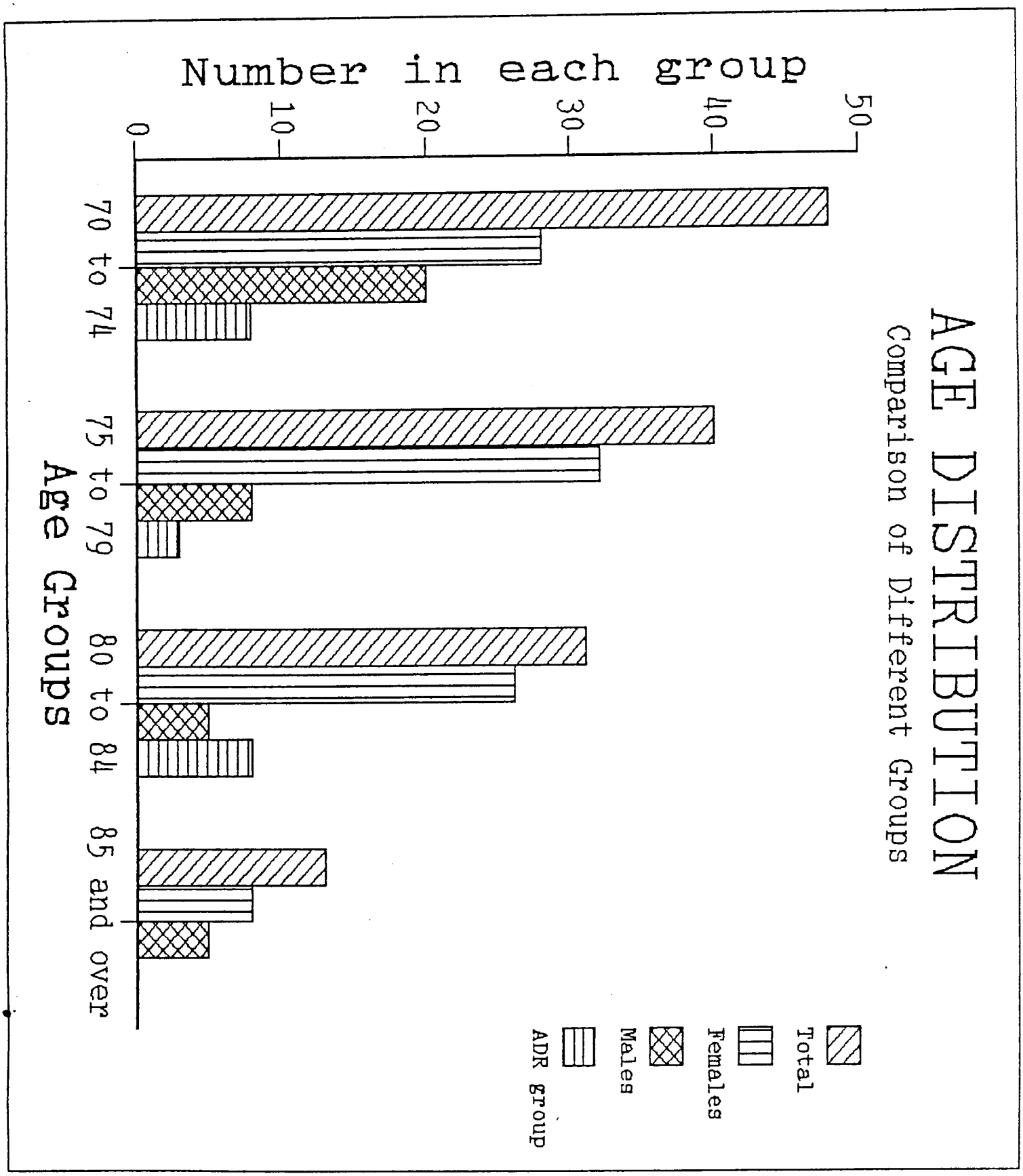
Age and sex distribution

The study group of 132 patients consisted of 94 females and 38 males, comprising 72 and 28 percent of the total sample respectively. The average age of the whole group was 77,6 years, with a standard deviation (SD)of 5,3 years. The female group had an average age of 77,7 years (SD of 4,9), while the average age of males was 77,1 years (SD of 6,1).

Of the 132 patients, 19 were noted to have experienced an adverse drug reaction (ADR). No patient had more than a single ADR. The average age of the ADR group was 76,9 years (SD of 4,12) and the average age of the non-ADR group was 77,7 years (SD of 5,8).

Figure 3.1 (shown overleaf) is a graphic representation of the age and sex characteristics of the total study population, and the age distribution of the ADR group. This latter group was not subdivided into male and female, as only one of the ADR group was male.

Figure 3.1


AGE DISTRIBUTION
Comparison of Different Groups
Number in each group
0
10
20
30
40
50
70 to 74
75 to 79
80 to 84
85 and over
Age Groups
Total
Females
Males
ADR group

Disease characteristics of the study group

A total of 419 conditions were identified in the study group, this giving an average of 3,2 problems per patient. The age and sex distribution of these problems is shown in Table 3.1.

Table 3.1: Age and sex distribution of problems

Age group	*Sex*	*Problems per patient*
65 - 75	Male	2,5
	Female	3
Over 75	Male	3,5
	Female	3,7

A graphic representation of the relative contribution of the different diagnostic classes to the total number of problems is shown overleaf in Figure 3.2, and a more detailed numerical analysis follows in Table 3.2.

Figure 3.3 is a histogram showing the average number of diseases in each age group from 70 to 94 years. Due to lesser numbers of old patients, 85 to 89 year olds were grouped together, as were the 90 to 94 year olds. Spearman's Rank Correlation Coefficient[29] showed no significant association between increasing age and number of diseases (r_s = 0.1092).

Figure 3.2

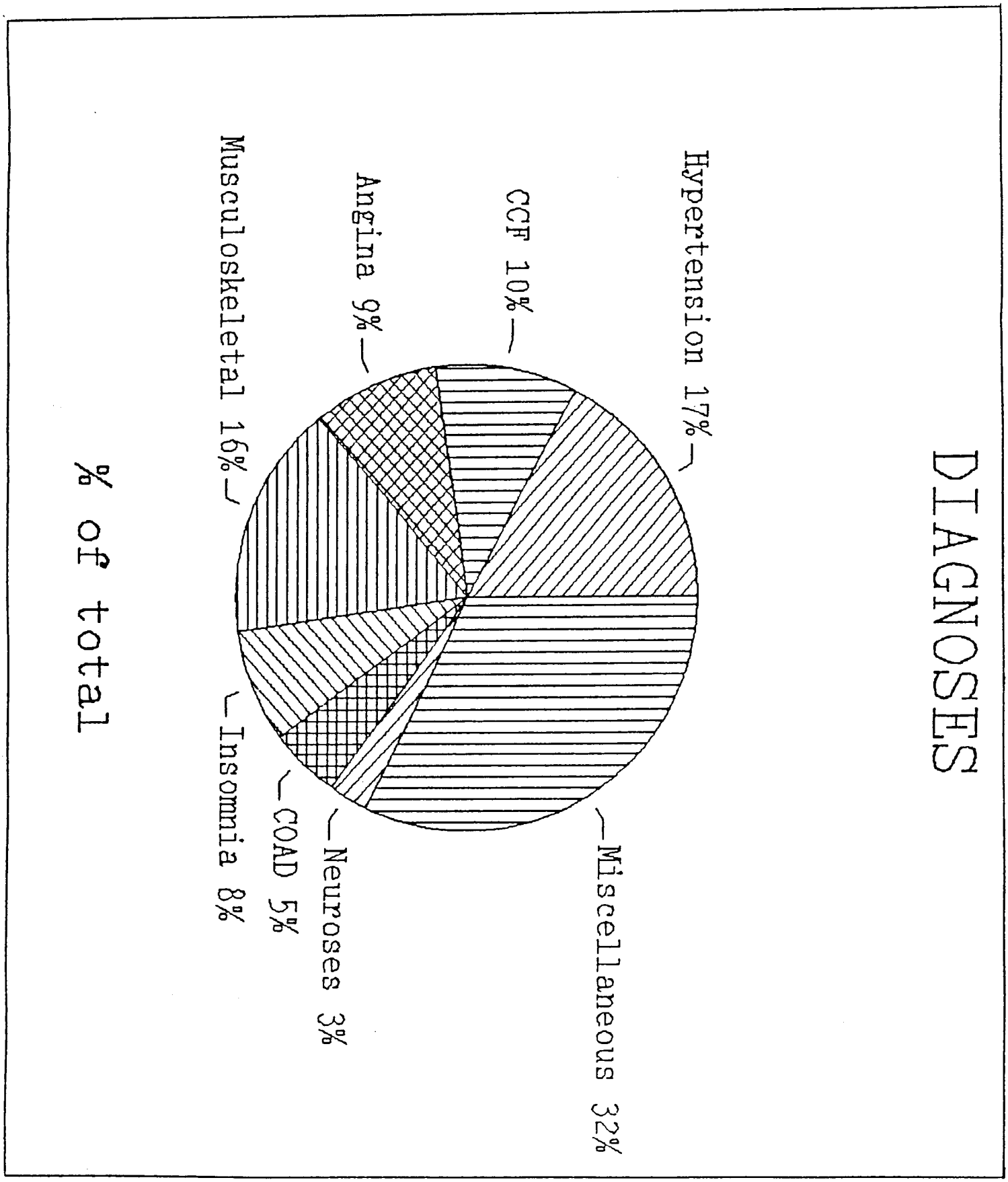
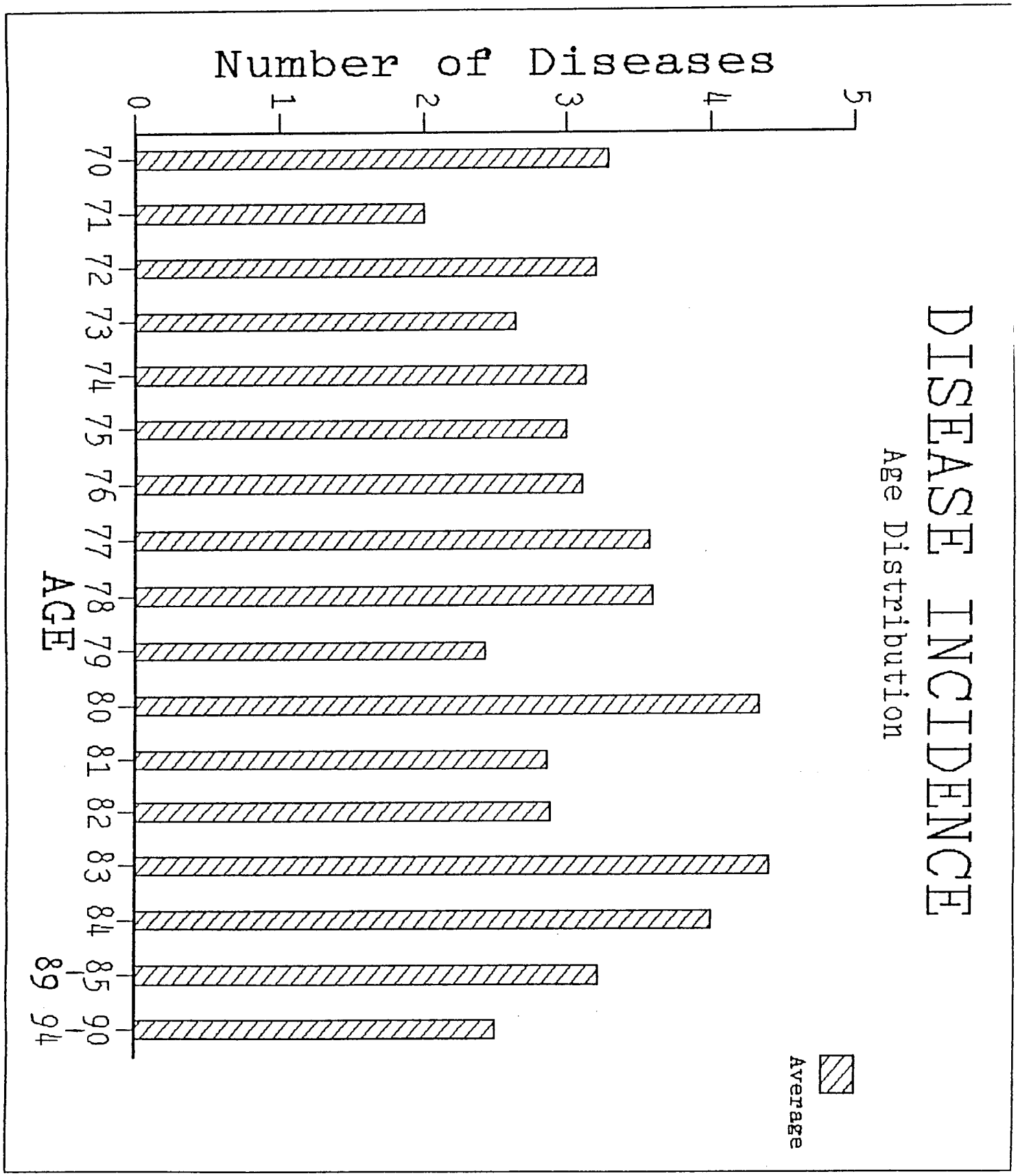

DIAGNOSES
% of total
Hypertension 17%
CCF 10%
Angina 9%
Musculoskeletal 16%
Insomnia 8%
COAD 5%
Neuroses 3%
Miscellaneous 32%

Table 3.2: Major presenting problems

CONDITION	*PREVALENCE*	*% OF TOTAL PROBLEMS (% of 419)*	*% OF TOTAL PATIENTS (% of132)*
Hypertension	73	17	55,3
Congestive Cardiac Failure	43	10	32,6
Ischaemic Heart Disease	37	9	28,0
Musculoskeletal Disorders	65	16	49,2
Insomnia	34	8	25,8
Chronic Obstructive Airways Disease	21	5	15,9
Anxiety and/or Depression Neuroses	12	3	9,1
Vertigo and Dizziness	9	2	6,8
Miscellaneous	125	30	94,7
TOTAL	419	100	317,4

Figure 3.3


DISEASE INCIDENCE
Age Distribution
Number of Diseases
0
1
2
3
4
5
AGE
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
89
90
94
Average

Drugs prescribed

It was assumed that patients were taking their medication as prescribed. A graph of the numbers of drugs prescribed to different sub-groups of patients is shown in Figure 3.4.

A total of 603 drugs were prescribed, giving an average of 4,6 drugs per patient (SD = 1,6), and a ratio of 1,44 drugs per condition being treated. Females received an average of 4,7 drugs (SD = 1,6) and males an average of 4,3 (SD = 1,7). The ADR group received an average of 4,3 drugs per patient (SD = 1,6). Thus the ADR group received on average fewer drugs than the total group, although this difference was not statistically significant. A subgroup of 32 patients who had been taking their medication unchanged for a period of 12 months or longer without experiencing any recorded adverse reactions, received an average of 3,8 items/patient

Figure 3.5. shows the average number of drugs prescribed in each age group. Spearman's Rank Correlation Coefficient[29] indicated that there was no significant association between age and the number of drugs prescribed (r_s = 0,0421)

A graphic representation of the relative amounts prescribed in the different drug classes is shown in Figure 3.6, with a more detailed description in Table 3.3. The major drug classes used are summarized in Table 3.4.

Figure 3.4

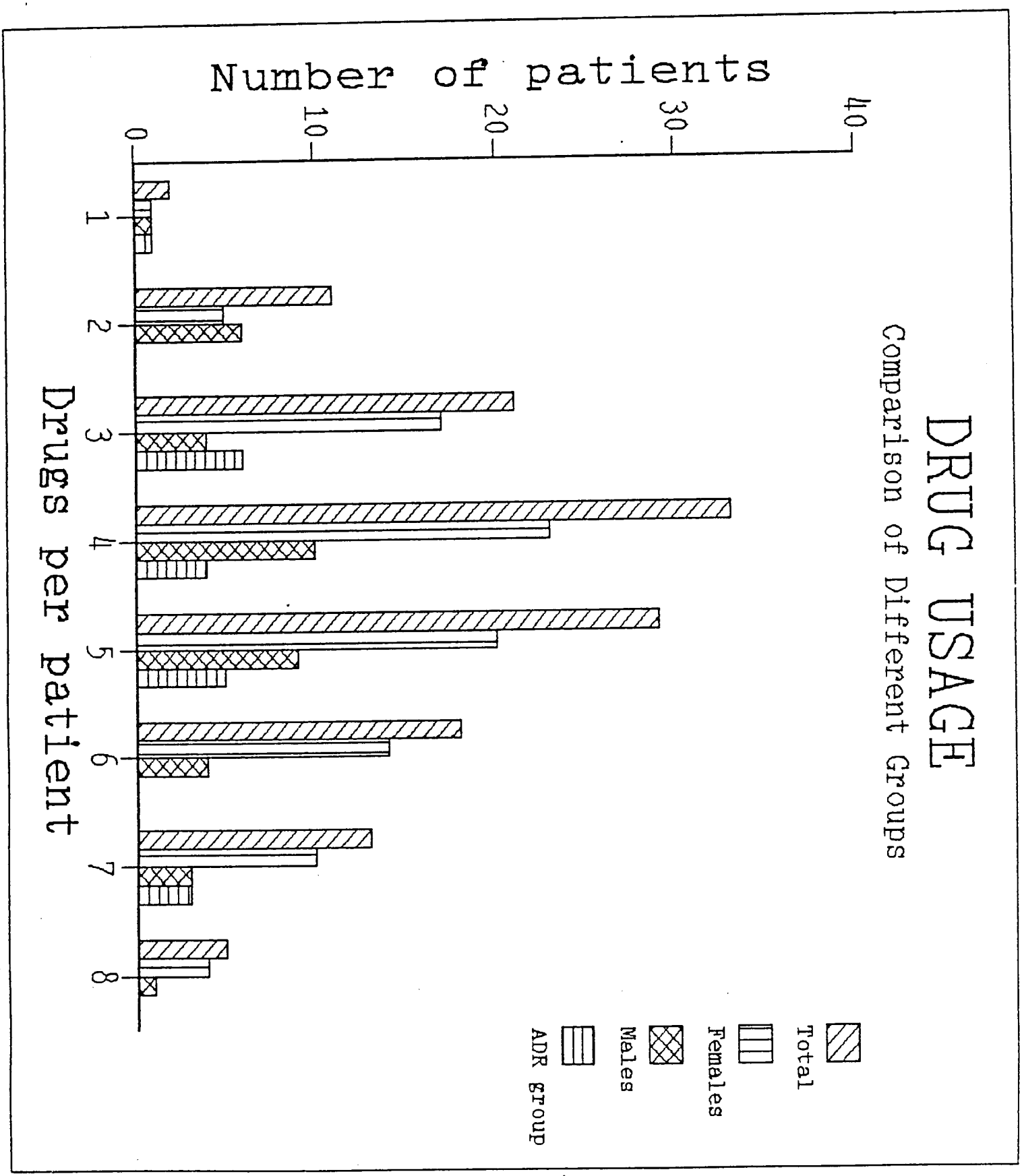

DRUG USAGE
Comparison of Different Groups
Number of patients
0
10
20
30
40
Drugs per patient
1
2
3
4
5
6
7
8
Total
Females
Males
ADR group

Figure 3.5

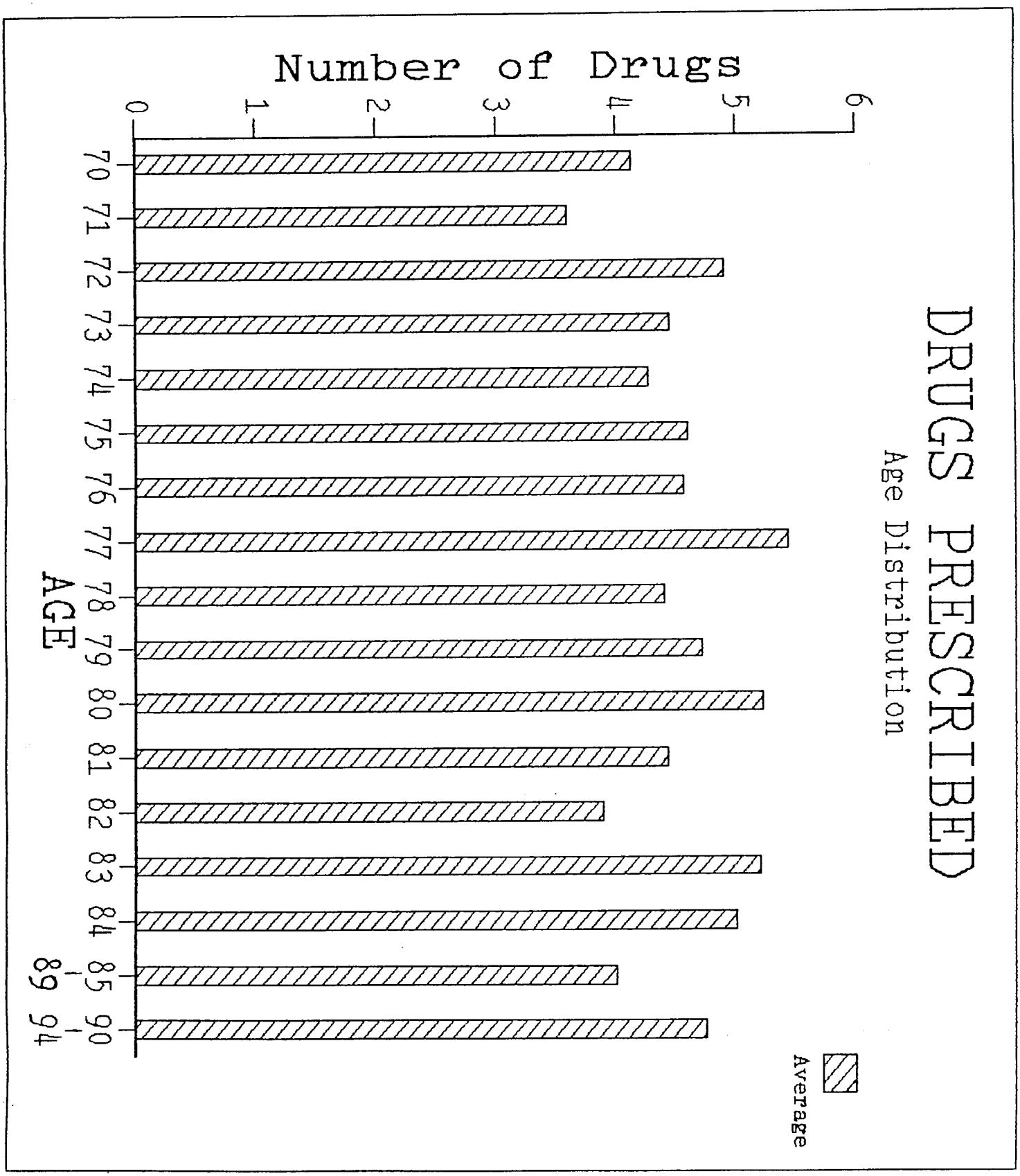

Number of Drugs
0
1
2
3
4
5
6
AGE
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
89
90
94
DRUGS PRESCRIBED
Age Distribution
Average

Figure 3.6

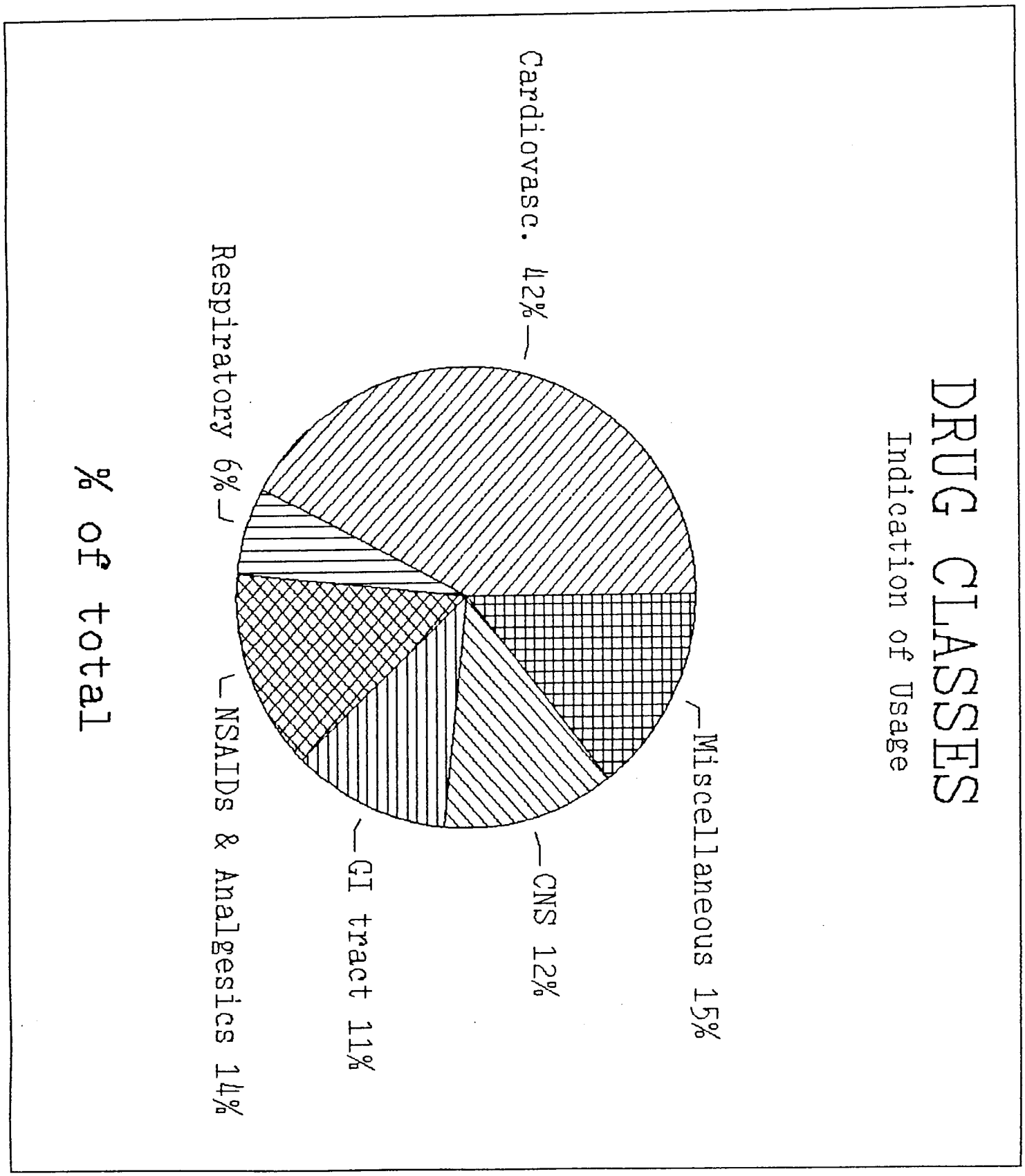

DRUG CLASSES
Indication of Usage
Cardiovasc. 42%
Respiratory 6%
Miscellaneous 15%
CNS 12%
GI tract 11%
NSAIDs & Analgesics 14%
% of total

Table 3.3: Drugs prescribed (603 drugs)

DRUG	*FREQUENCY*
Cardiovascular System(including diuretics).	Total:254
Amiloride,hydrochlorothiazide	43
Cyclopenthiazide	29
Furosemide	23
Potassium supplements	19
Digoxin	26
	10
Propanolol	6
Oxprenolol	5
Verapamil	3
Nifedipine	4
Glyceryl trinitrate	14
Isosorbide dinitrate	22
Indapamide	2
Methyldopa	28
Prazosin	9
Hydrallazine	2
Hydroflumethiazide,rauwolfia,KCl	9
Respiratory System	Total:37
Salbutamol inhaler	13
Salbutamol tabs	3
Xanthine bronchodilators	12
Compound cough preparations	9

Gastro-intestinal Tract	Total:63
Antacids (various)	28
Cimetidine	2
Sucralfate	1
Stimulant laxatives	17
Bulk-forming drugs	11
Hyoscine butylbromide	4
Central Nervous System	Total:74
Diazepam	24
Oxazepam	6
Nitrazepam	17
Temazepam	1
Lorazepam	1
Tricyclic antidepressants	8
Prochlorperazine	6
Cinnarizine	5
Phenobarbitone	3
Carbamazepine	1
Levodopa, benzerazide	1
Haloperidol	1
Analgesics and Non-steroidal Anti-inflammatory Drugs	Total:86
Paracetamol	33
Dextropropoxyphene	9
Diclofenac	22
Ibuprofen	7
Naproxen	4
Sulindac	4
Indomethacin	3
Piroxicam	2
Fenoprofen	1
Mefenamic acid	1

Miscellaneous	Total: 89
Vitamin preparations	24
Allopurinol	4
Thyroxine sodium	3
Low dose aspirin	4
Dipyridamole	6
Quinine sulphate	5
Chlorpropamide	3
Calcium supplements	3
Other*	37

*includes artificial sweeteners, decongestants, urinary antiseptics, and short courses of antibiotics

Table 3.4: The most frequently prescribed classes of drugs

DRUG	*FREQUENCY*	*% OF 603 DRUGS*	*% OF 132 PATIENTS*
1. Diuretics	95	15,7	71,9
2. Antihypertensives*	50	8,3	37,8
3. Benzodiazepines	49	8,1	37,1
4. Nonsteroidal anti-inflammatory drugs	44	7,3	33,3
5. Coronary vasodilators+	43	7,1	32,5
6. Analgesics	42	7,0	31,8
7. Antacids	28	4,6	21,2
8. Laxatives	28	4,6	21,2
9. Bronchodilators	28	4,6	21,2
10. Digoxin	26	4,3	19,7
11. Vitamins	24	4,0	18,2
12. Potassium supplements	19	3,2	14,4

* excluding diuretics, including beta-blockers

+ both nitrates and calcium-channel blockers

Adverse drug reactions

Adverse drug reactions were noted in 19 patients, and these are detailed in Table 3.5. As far as could be ascertained, none were severe enough to require admission, although in all instances the offending drug was discontinued.

Table 3.5: Adverse drug reactions

DRUG AND DOSAGE	*ADVERSE REACTION*	*INCIDENCE*	*% OF TOTAL**
Diuretics			
Amiloride/hydrochlorthiazide 2 daily	Muscle cramps	3	6,9
Furosemide 80 mg daily	Muscle cramps	3	13,0
Beta Blockers			
Oxprenolol 80 mg b.d.	Intermittent claudication	1	33,3
Atenolol 50 mg daily	Symptomatic bradycardia	2	20,0
Atenolol 50 mg daily	Cardiac failure	2	20,0
Centrally acting antihypertensive agents			
Methyldopa 250 mg b.d.	Postural hypotension	1	3,6
Cardiac glycosides			
Digoxin 0,25 mg daily	Nausea and vomiting	3	11,5
Non-steroidal anti-inflammatory drugs			
Diclophenac 25 mg t.d.s.	Dyspepsia	2	9,0
Indomethacin 25 mg t.d.s.	Dyspepsia	1	33,3
Indomethacin 25mg t.d.s.	Peptic ulcer	1	33,3

*Adverse reactions as a percentage of total prescriptions for the drug

Table 3.6 shows a comparison between the total group, the ADR group and the non-ADR group in respect of age, diseases and number of drugs. Inspection of the averages and their associated standard error shows overlap between all three groups for each of the above parameters. There is therefore no statistically significant difference between the three groups as regards age, diseases detected or number of drugs prescribed.[30]

Table 3.6: Comparison of the total, the non-ADR and the ADR groups

		AGE	DISEASES	DRUGS
** TOTAL GROUP ** (132 patients)				
	TOTALS:	10237	419	603
	AVERAGE:	77.55	3.17	4.57
	VARIANCE:	27.94	1.85	2.58
	STD DEV:	5.29	1.36	1.61
	STANDARD ERROR:	0.46	0.15	0.14
Females:94				
	FEMALE AVERAGE:	77.73	3.29	4.68
	FEMALE STD DEV:	4.93	1.42	1.58
Males:38				
	MALE AVERAGE:	77.11	2.89	4.29
	MALE STD DEV:	6.14	1.18	1.66
** NON-ADR GROUP ** (113 patients)				
	TOTALS:	8776	352	522
	AVERAGE:	77.66	3.12	4.62
	VARIANCE:	29.87	1.60	2.59
	STD DEV:	5.47	1.27	1.61
	STANDARD ERROR:	0.51	0.12	0.15
** ADR GROUP ** (19 patients)				
	TOTALS:	1461	67	81
	AVERAGE:	76.89	3.53	4.26
	VARIANCE:	16.99	3.37	2.54
	STD DEV:	4.12	1.84	1.59
	STANDARD ERROR:	0.95	0.42	0.37

Drug efficacy

Using criteria of efficacy as outlined on page 13, the prescribed drugs were assessed as being effective in 83 patients, or 63 % of the total sample. 57% of females and 76% of males appeared to benefit from treatment. In 44 patients (33% of total) it was not clear whether they benefitted: 37% of females and 24% of males were in this group. 5 patients (4% of total) appear not to have benefitted: all these patients were female and comprised 5% of all females.

In the ADR subgroup, 11 patients (58% of the ADR group) were assessed as having benefitted from their treatment, either until or despite the appearance of a side-effect. In the remaining 42% of this group efficacy was uncertain, but none of these patients appear to have shown no benefit from therapy.

The data on drug efficacy appears graphically in Figure 3.7

In a subgroup of 32 patients who had been on unaltered medication for at least twelve months, and who had not experienced any adverse reaction whilst on this medication, treatment was assessed as having a beneficial effect in 81% of these patients, and was of uncertain effectiveness in the remaining 19%. The drugs that these patients were on are listed in Table 3.7

Figure 3.7

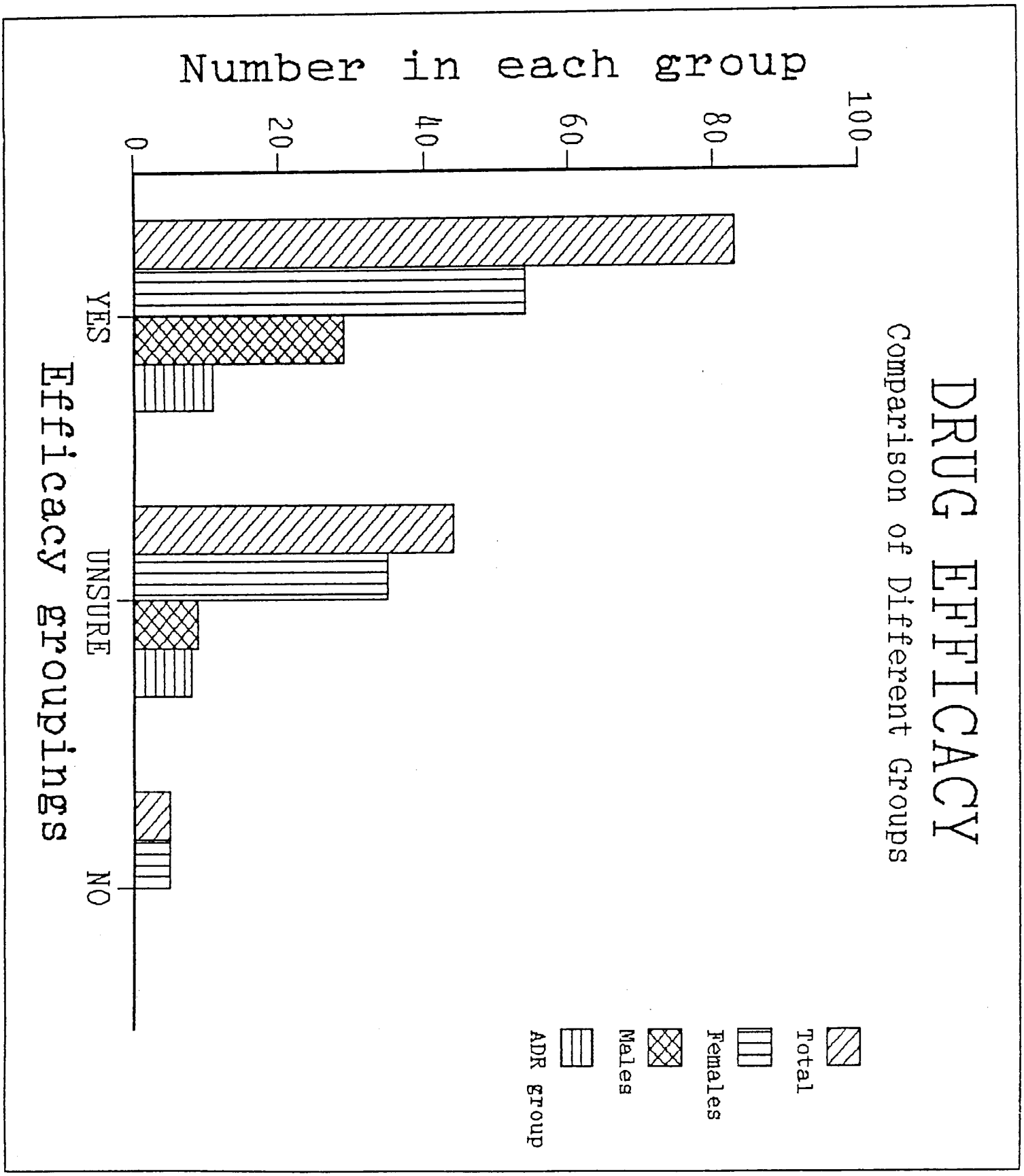

DRUG EFFICACY
Comparison of Different Groups
Number in each group
0
20
40
60
80
100
YES
UNSURE
NO
Efficacy groupings
Total
Females
Males
ADR group

Table 3.7: Well tolerated drugs in a stable sub-group

The following drugs, in the dosages indicated, were identified as being well tolerated in the thirty-two patients who had been on unaltered prescriptions for at least twelve months, without any adverse reaction being recorded:

DRUG	*DOSE*	*FREQUENCY*
Cardiovascular System		
Digoxin	0,125 mg daily	8
Oxprenolol	160 mg daily	1
Atenolol	100 - 200 mg daily	2
Propanolol	30 - 60 mg daily	2
Isosorbide dinitrate	10 - 80 mg daily	4
Glyceryl trinitrate	0,5 mg p.r.n.	2
Furosemide	40 - 120 mg daily 40 mg twice weekly	11 1
Slow release KCl	2 - 6 tabs daily	8
Spironolactone	50 mg daily	1
Amiloride, hydrochlorothiazide	1 - 2 daily	7
Cyclopenthiazide, KCl	1 - 2 daily	6
Hydrochlorothiazide	20 mg daily	1
Hydroflumethiazide, rauwolfia, KCl	1 - 3 tabs daily	4
Methyldopa	500 - 750 mg daily	2
Prazosin	5 mg b.d.	1
Nifedipine	20 mg t.d.s.	1

Respiratory System		
Theophylline syrup	120 - 180 mg t.d.s.	2
Aminophylline suppositories	1 nocte	1
Salbutamol inhaler	2 - 8 puffs daily	4
Salbutamol tablets	2 - 12 mg daily	3
"Nethaprin Dospan"™	2 nocte	1
Gastro-intestinal Tract		
Cimetidine	400 mg nocte	1
Sennoside B	7,5 - 22,5 mg nocte	3
Sterculia, frangula	10 mls daily	4
Antacids (various)	various	4
Central Nervous System		
Trimipramine	30 mg daily	1
Hydroxyzine	10 -30 mg daily	2
Diazepam	2 - 10 mg daily	6
Nitrazepam	5 mg daily	2
Oxazepam	10 - 25 mg daily	3
Butobarbitone	200 mg nocte	1
Miscellaneous		
Thyroxine sodium	0,2 mg daily	1
Prednisone	5 mg alt days	1
Vitamins (4 preparations)	various	4

CHAPTER FOUR

DISCUSSION

The study described in this dissertation was undertaken in order to establish whether the theoretical limitations to effective long-term polypharmacy in the elderly resulted in recorded morbidity in a group of elderly outpatients. The findings of this study have to be interpreted in the context of the type of patients seen at a general outpatient department, from which group a relatively small sample was drawn. Data from the sample studied suggests that polypharmacy is generally well tolerated and benefits the majority of patients.

This conclusion is based on the fact that overall, 63% of patients were assessed as having benefitted symptomatically from the medication prescribed, whilst in only 4% was there lack of efficacy; the remainder being uncertain. Thus, whilst well over half of the patients appeared to benefit from their treatment, only 14,4% of the patient sample experienced recorded adverse reactions, all of which were relatively minor and were relieved by stopping or altering the offending medication. These results suggest that where multiple medication for multiple ailments is required, it is

generally likely to be of symptomatic benefit to the patient, and therefore should not be withheld on mainly theoretical grounds. This is in accordance with current medical practice.

As indicated in the previous chapter, there was no significant difference in the average age, number of diseases, or number of drugs prescribed between the ADR group, the non-ADR group, and the total sample. This suggests that, in patients over the age of 70 years, these parameters are not predictors of the likelihood of an ADR.

Comparison with other similar studies

A search of the available literature has not revealed any study that attempts to assess the effectiveness of multiple medication prescribed to the elderly in the outpatient setting, whilst only two studies have been found which deal with the overall incidence of adverse drug reactions in ambulatory older patients.

Klein et. al.[31] used telephonic interviews in a randomly selected group of 299 medical outpatients to investigate how often these patients linked untoward symptoms with their medication. 107 of their patients were 65 years and over, and in these patients, who were prescribed an average of 2,9 medications each, the mean number of side-effects reported

was 0,37 per person, compared to 0,14 in our study. However the study methodologies are not comparable, as Klein's method used direct leading questions which covered a range of possible side-effects and could conceivably have resulted in an over-reporting of non-specific symptoms that in fact were not causally related to medication use.

In a recent in-home survey[32] of 155 ambulatory elderly patients with a mean age of 71,6 years (vs 76,3 in our study), the average reported number of medical problems was 3,8 per person (vs 3,2) and the average number of prescribed drugs being taken was 4,5 per person (vs 4,6). A history of adverse or allergic reactions to one or more drugs was common and was reported by 29,1% of respondents. Aspirins were the most common offenders and accounted for 13 % of the adverse effects. These aspirins appear to have been non-prescription medication, and were acquired by the patients as over the counter drugs (OTC's). Our study did not assess OTC's, and no aspirin side-effects were noted in our sample. If the adverse reactions to aspirin in the above series are not considered, there remains a 16,1% incidence of side-effects, which is comparable to the 14,4% incidence in our series. Their list of commonly found drugs was similar in certain respects to ours: 48% (vs 72%) of their patients were on diuretics, 17% (vs 14%) on potassium supplements, 36% (vs 21%) on laxatives, and 33% (vs 21%) on antacids.

Discussion of specific classes of drugs

The findings of our study support the view that polypharmacy can benefit ambulatory elderly patients, and therefore what is needed is not an empirical reduction in the number of items prescribed, but rather skilled and knowledgeable prescribing practices. Those who presribe for elderly patients should fully appreciate that the use of any drug is governed by a consideration of its indications and its likely therapeutic index in a given patient, and that the assessment of this is often more difficult in the older patient because of the increased inter-individual variability for some parameters that occurs with advancing age,[73] and also because of the altered presentation of some disorders in the elderly.[74] Other factors such as patient compliance and the cost of medication must also be considered when the clinician is contemplating multiple drug therapy.

The sample size used in this study is too small to draw definitive conclusions about drugs or dosages that should be avoided in the elderly,[33] but the agents that were noted to cause side-effects in this study will be detailed further below with reference to other reports of their potential toxicity in the elderly. In this study, a total of 607 items were prescribed, 19 of which caused side-effects. These 19 items were however confined to only 5 classes of drugs, which will now be dealt with in turn.

DIURETICS

The diuretics were the most frequently used class of drugs in this study, with 71,9 % of our patients receiving diuretics. Other studies have also shown that diuretics are the most frequently prescribed drugs in the elderly,[31,32,34,35] and this presumably reflects the high incidence of cardiovascular problems in the elderly, with hypertension and congestive cardiac failure being the two most common disorders treated in our study. Possibly reflecting this frequent use, diuretics were the most common cause of side-effects in our study, resulting in six reports of muscle cramps; three from furosemide and three from an amiloride/hydro-chlorothiazide combination. Although serum electrolyte levels were not checked in these patients, it is probable that hypokalemia was responsible for the muscle cramps. Electrolyte abnormalities, notably hypokalemia, are well recognized side-effects of both loop and thiazide diuretics.[36,37] The elderly are at particularly high risk for hypokalemia, as aging is associated with a reduced potassium intake.[13]

It has been suggested that diuretic induced potassium depletion might predispose to fatal cardiac arrythmias in certain patients prone to such arrythmias.[38] Hypokalemia can also potentiate digoxin toxicity, which is a problem that will be discussed further below. Other problems which have been noted with diuretics, including impaired glucose

tolerance, increased serum uric acid, changes in serum lipids and impotence,[39] were not detected in our study.

A study which evaluated a group of 27 elderly persons in a nursing home who were on long-term diuretics, found that in 5 cases there were no clinical notes giving the reason for diuretic therapy; in 12 patients the diuretics had been given for an initial indication such as hypertension or congestive cardiac failure, but the indication had subsequently never been re-evaluated; and in the remaining 10 diuretics had been given for pedal oedema, likewise without re-assessment.[40] At the start of the study, no indications for continuing the diuretics could be found in all 27 patients, so the diuretics were stopped and subsequent follow-up revealed no need for them as long-term therapy. Four patients benefited from the cessation of diuretics: in 2 dizziness related to postural hypotension was no longer a problem, and 2 others regained control of micturition. This nursing home study shows that even though diuretic therapy appeared to be effective, and only 14,8% of patients had side-effects related to diuretics, there is a great need to continually re-assess the need for all medication if ADR's are to be minimized. This study was exceptional regarding their ability to stop all drugs: in a study from two geriatric units it was possible to stop diuretics in patients admitted to hopsital in only 7 out of 13 cases, and in 4 they had to subsequently be restarted.[41]

BETA-ADRENOCEPTOR BLOCKING DRUGS

The complications of this class of drug that were noted in our study are well recognized and relate to their ability to block beta-adrenergic receptors.[42,43] A review of β-blockers in the elderly has reported that drug handling (apart from renal excretion) is not seriously affected by advancing age and adverse reactions are not significantly more common.[44] However any drug that causes hypotension either by redúcing vascular resistance or by depressing cardiac function may cause serious or disastrous consequences in the elderly, who are already somewhat volume depleted.[45] As ß-blockers decrease both vascular resistance and cardiac contractility, their indication in the individual patient must be carefully evaluated. The effect of age on the therapeutic effectiveness of β-blockers is hard to predict as age may influence not only pharmacokinetics, but also changes in the number and sensitivity of β-adrenoreceptors.[46]

In our study, 21 patients were on β-blockers and 5 ADR's presumably due to these agents were found: 160 mg of oxprenolol daily resulted in one report of intermittent claudication, whilst atenolol 50 mg daily was associated with two cases of symptomatic bradycardia and two cases of congestive cardiac failure. Hydrophilic β-blockers (such as atenolol) are excreted by the kidney, and there is a greater risk of toxicity with these agents in the eldery due to the

age-related decline in renal function, particularly in the presence of compounding factors such as dehydration which may be caused by concurrently prescribed diuretics. Propanolol, which is more lipophilic and is cleared by the liver, was given to 6 patients in our study without evidence of side-effects. However this cannot be seen in isolation: propanolol clearance is diminished in elderly subjects[47] and the Boston Collaborative Drug Surveillance program found a 12,4% toxicity rate in patients over the age of 60 years given propanolol, compared with a 5,6% incidence of toxicity in patients under the age of 50.[48]

CENTRALLY ACTING ANTIHYPERTENSIVE AGENTS

Methyldopa is effective in lowering blood pressure, is widely used, and is well tolerated by many elderly hypertensives.[49] The major side-effects are centrally mediated, and include sedation, dry mouth and postural hypotension.[50] In our study, only 1 out of 28 patients on methyldopa developed a related ADR, namely postural hypotension.

CARDIAC GLYCOSIDES

Digitalis use in the elderly is widespread[51] and in our study 26 patients (19,7% of the study population) were receiving digoxin; 9 of whom were in documented atrial fibrillation. The others were on digoxin for congestive cardiac failure.

There were two cases of digoxin toxicity in the 9 patients receiving the drug for atrial fibrillation, resulting in reduction of dosage, although serum levels were not done. Of the 17 patients on digoxin for cardiac failure, 1 patient became nauseous on 0,25 mg daily and this problem resolved when digoxin was stopped. In this group, 8 improved on their medication (other drugs including digoxin), 1 did not, and the outcome was uncertain in the remainder. Of the 9 patients on digoxin for atrial fibrillation, 5 improved and 4 were unsure.

The findings in our study regarding digoxin reflect in some ways the continuing debate regarding the appropriate use of this drug. Digoxin has a low therapeutic index and is a difficult drug to use in the elderly as underlying diseases and multiple-drug use tend to increase the danger of digoxin toxicity.[34] This may manifest in an unusual fashion, for example, depression or anorexia. Furthermore two-thirds of patients who are digoxin toxic may have blood levels close to or within the therapeutic range.[52]

Whilst there is little controversy with regard to the use of digoxin in certain supraventricular tachycardias, particularly in controlling the ventricular response rate in atrial fibrillation, its routine use in cardiac failure requires careful consideration. At least one study has shown that, in elderly patients who are in congestive heart failure with

normal cardiac rythm, digoxin clearly improved their left ventricular ejection fraction.[53] Some of these patients achieved maximal improvement in ejection fraction at serum digoxin concentrations of less than 1,0 ng/ml. However some studies have found that there are many patients on digoxin who do not benefit from it,[53,54] and in a re-evaluation of digitalis efficacy Mulrow and colleagues have concluded that "elderly patients with stable heart failure who have been managed chronically with digoxin may warrant a closely monitored trial of withdrawal of digoxin therapy."[55] In our study, one patient who developed digoxin toxicity had the drug withdrawn without the development of problems. Two patients who were digoxin toxic on 0,25 mg daily tolerated 0,125 mg daily without side-effects. It follows that where long-term digoxin therapy is needed, it should be used in the lowest dose that is effective in a given patient.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

It is well recognised that the NSAIDs as a group are associated with a high incidence of adverse reactions, and many of these are more common and more serious in the elderly.[56,57] The experience with benaxoprofen, which resulted in the death of a number of elderly patients, was related to age related pharmacokinetic changes which resulted in decreased renal elimination of this drug, with the consequent high serum concentrations leading to renal and

hepatic failure.[58] The need for caution with NSAIDs is now well known, and guidelines for dosage adjustment in the elderly are available.[59] Adverse reactions associated with NSAID use in the elderly include indigestion, gastric ulceration, renal impairment with sodium retention, ankle oedema and precipitation of cardiac failure, interference with antihypertensive agents, blood dyscrasias, and cognitive impairment.[60,61]

In our study 33% of the patient sample were receiving NSAIDs. Of these 44 patients, four (9%) experienced NSAID related ADRs: 75 mg of diclophenac daily resulted in two reports of dyspepsia, and 75 mg of indomethacin daily resulted in one report of dyspepsia and one of peptic ulceration. Guidelines to minimize the occurrence of ADRs from NSAIDs in high risk patients have been published.[62] They include: begining therapy with the least potent NSAID or other types of analgesic agents; the use of an appropriate NSAID in a dose that allows for factors such as renal impairment; the measurement of baseline serum creatinine and electrolyte levels with subsequent repeat monitoring, especially if antihypertensive or diuretic medications are added; and asking patients to weigh themselves daily.

Comments on some frequently prescribed drugs that were not associated with recorded side-effects in our study

Benzodiazepines

Where sedative-hypnotic drugs are required in the elderly, benzodiazepines are commonly used[63] and are generally safe , although older patients must be monitored closely for the development of excessive drowsiness or ataxia as agents with long half-lives reach steady-state levels.[64] In one study of 257 ambulatory geriatric patients, 36,1% of their study population used benzodiazepines, and the authors concluded that "that there was no evidence that any subject had become addicted....it appears that in this age group , prolonged use of benzodiazepines at low doses, with the patients regulating the quantity, is safe and may be helpful."[65]

The benzodiazepines were the third most frequently prescribed drugs in our study, and were being used without recorded morbidity by 37,1 % of the study population. Of the 49 prescriptions for benzodiazepines, 24 were for diazepam and 17 for nitrazepam. Although both of these agents have prolonged half-lives in the elderly,[66] all the benzodiazepines were used in low dosages and this may account for the absence of side-effects in our study.

Paracetamol

Changes in the pharmacokinetics of paracetamol in the elderly have been documented, but they are not significant enough to require dose adjustment.[2] There is a risk of hepatotoxicity when used in supratherapeutic doses, particularly in the presence of chronic liver disease, but in therapeutic doses paracetamol appears to be a relatively safe analgesic for use in the geriatric population.[58] 33 of our patients were on paracetamol without the appearance of adverse reactions.

Antacids

It has been reported that hiatus hernia, gastritis and gastric ulcer are more common in the elderly.[67] In a large study comprising just over 3 000 elderly ambulatory patients, 13% of men and nearly 19% of women used antacids.[68] Side-effects noted included constipation from aluminium containing preparations and diarrhoea from calcium carbonate compounds. In our study, 28 patients (21,2% of the group studied) were receiving regular antacids without obvious side-effects. The indications for the antacids appeared to be dyspepsia, or hiatus hernia in a few patients. Thirteen of the patients receiving antacids were on NSAIDs.

Drug interactions

When two or more drugs are administered concurrently or within a reasonable period of each other, the result may be indifference, synergism, potentiation, or antagonism.[69] This may occur because of interactions at a physicochemical, pharmacokinetic or pharmacodynamic level.[70] With long-term polypharmacy, probably the most important drug interactions are the blunting of the effects of one drug by another (such as the antagonism of a diuretic by a NSAID), and the predisposition to the side-effect of one drug by the use of another (such as when diuretic induced hypokalemia predisposes to digoxin toxicity). It has been estimated that in the ambulatory elderly, about 6% of patients might be affected by drug-drug interactions, although in nursing homes, with 4 to 9 drugs per patient per day, they may account for 22% of all ADRs reported.[69]

In our study, two of the patients who experienced digoxin toxicity were also on thiazide diuretics, which could have predisposed these patients to the digoxin toxicity. Three other patients who experienced dizziness and postural hypotension related to the introduction of an additional anti-hypertensive agent were in fact already on diuretics, and therefore the ADR attributed to the additional agent may really have reflected a summation of side-effects. Thus, in our study, 5 out of 19 ADRs were possible drug-drug

interactions (26,3%). Looked at in another way, 3,8% (5 out of 132 patients) of the study population had an ADR which may have largely been due to a drug-drug interaction.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

This study has found that degenerative, largely unavoidable conditions such as hypertension, congestive cardiac failure, ischemic heart disease and musculoskeletal disorders were common amongst a group of ambulatory elderly patients, and these diseases were managed with a variety of drugs. This study contributes to our understanding of polypharmacy in the elderly, as it was based on a random group of elderly ambulatory patients, and both the benefits (efficacy) and adverse effects of drug therapy were evaluated. This differs from many other studies of ADRs in the elderly, in which only those ADRs resulting in hospital admission were reported. Those studies, based on a selected inpatient sample, have not permitted an assessment of the incidence of such ADRs relative to the population at risk, nor have they permitted an evaluation of the benefit that the majority of patients might gain through polypharmacy.

The findings of this study indicate that polypharmacy does, in general, appear effective in controlling symptoms or even the disease processes in the population studied, and that the majority of patients benefitted from the therapeutic

intervention. Only a minority of patients experienced an ADR, which tended to be relatively benign and reversible on discontinuing the offending medication. These findings support the observation that "drugs are probably the most cost-effective modality of chronic disease management."[71]

At the same time it must be remembered that every patient who suffers an adverse drug reaction is unlikely to find much consolation in the fact that the statistical majority benefitted. Accordingly, studies such as this attempt to identify prescribing practices that are safe and effective, and also draw attention to problem areas where the use of certain drugs must be particularly carefully evaluated. In the previous two chapters, details have been provided of some of the drugs that were prescribed most frequently in this study group, with particular reference to those agents that were associated with side-effects. However, due to the relatively small numbers of patients studied, the range of side-effects found was small, and they are really more of relevance as components of a general strategy to minimize adverse drug reactions in the elderly.

Although polypharmacy can be beneficial, the possibility of an ADR places an onus on the prescriber to review the indications for each drug in a given patient on every occasion that it is prescribed. The prescription of a drug may often be an unfortunate physician response to a

patient's ill-defined symptoms, and an inappropriate substitute for comprehensive assessment of the patients physical, psychological and social well-being. Because it is generally easier to prescribe medication, there tends to be little enthusiasm for other therapeutic modalities such as rehabilitative or environmental intervention. The patient, trying to face the deprivations and deal with the demands of the aging process, may benefit more from an educator, guide and philosopher than from an ill-conceived, costly and potentially toxic assortment of pills.

Where it is felt that the use of medication is the most appropriate form of treatment, the prescriber needs to be well informed about the drugs to be used. Particularly relevant in the geriatric patient is a knowledge of the drug's likely pharmacokinetics and pharmacodynamics in the presence of age and disease, and the possibly altered manifestations of drug toxicity in the elderly patient.

Fortunately the need for this kind of knowledge is now recognised, and research in this field is ongoing. Studies such as this one could be extended to form part of the ongoing evaluation of drug therapy in elderly ambulatory patients. Information on drug efficacy and the incidence of side-effects would be useful as a component in auditing the quality of geriatric health care, whilst data on individual drug side-effects could assist in maintaining an ongoing

awareness of potential pit-falls in drug treatment of the elderly. A real-time prospective entry of patient prescriptions and relevant clinical data into a computer data base would not only ensure the collection of a large amount of data which could be of benefit in the detection of previously unsuspected ADRs and drug-drug interactions, but would also screen prescriptions for known drug-disease and drug-drug interactions.

The use of modern technology is however only an aid, and not a substitute for a knowledgeable physician and the use of sound clinical judgment in the effective management of diseases in the elderly. The factors that need to be considered in using drug therapy in the aged have been thoroughly detailed in a 10 page report by an expert committee of the Royal College of Physicians of London.[72] In this report the need for careful clinical assessment, the simplification of the dose and drug regime as far as possible, and good communication between the patient and members of the health care team are emphasized. These points, together with a sound appreciation of clinical pharmacology in the elderly, provide a basis for the more effective and safer use of drugs in the older patient.

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Appendix 1

GERIATRIC POLYPHARMACY PROJECT

DATA COLLECTION SHEET

A. Patient Folder No.

B. Age:

C. Race: D. Sex:

E. Number of disease processes being treated:

F. Medication: Drug and dosage:

1.	11.
2.	12.
3.	13.
4.	14.
5.	15.
6.	16.
7.	17.
8.	18.
9.	19.
10.	20.

G. Length of time (in months) patient has been on this identical prescription:

H. If less than six months' indicate reasons for change eg. side effects, therapeutic failure, appearance of new disease process:
(free text)

I. If side-effects (drug reactions) are the answer to question (H) indicate responsible drugs. Indicate whether drug reaction (DR) or drug-drug interaction (D -DI):

1.
2.
3.
4.
5.

Comments: eg. 6/60, 12/60 shows low potassium

J. Does the patient's present prescription appear to be therapeutically effective?

YES / NO / UNSURE.